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NEWS	1		Web Page URLs for STN Seminar Schedule - N. America
NEWS	2	Apr 08	"Ask CAS" for self-help around the clock
NEWS	3	Apr 09	BEILSTEIN: Reload and Implementation of a New Subject Area
NEWS	4	Apr 09	ZDB will be removed from STN
NEWS	5	Apr 19	US Patent Applications available in IFICDB, IFIPAT, and
IFIUDB			
NEWS	6	Apr 22	Records from IP.com available in CAPLUS, HCAPLUS, and
ZCAPLUS			
NEWS	7	Apr 22	BIOSIS Gene Names now available in TOXCENTER
NEWS	8	Apr 22	Federal Research in Progress (FEDRIP) now available
NEWS	9	Jun 03	New e-mail delivery for search results now available
NEWS	10	Jun 10	MEDLINE Reload
NEWS	11	Jun 10	PCTFULL has been reloaded
NEWS	12	Jul 02	FOREGE no longer contains STANDARDS file segment
NEWS	13	Jul 22	USAN to be reloaded July 28, 2002; saved answer sets no longer valid
NEWS	14	Jul 29	Enhanced polymer searching in REGISTRY
NEWS	15	Jul 30	NETFIRST to be removed from STN
NEWS	16	Aug 08	CANCERLIT reload
NEWS	17	Aug 08	PHARMAMarketLetter(PHARMAML) - new on STN
NEWS	18	Aug 08	NTIS has been reloaded and enhanced
NEWS	19	Aug 19	Aquatic Toxicity Information Retrieval (AQUIRE) now available on STN
NEWS	20	Aug 19	IFIPAT, IFICDB, and IFIUDB have been reloaded
NEWS	21	Aug 19	The MEDLINE file segment of TOXCENTER has been reloaded
NEWS	22	Aug 26	Sequence searching in REGISTRY enhanced
NEWS	23	Sep 03	JAPIO has been reloaded and enhanced
NEWS	24	Sep 16	Experimental properties added to the REGISTRY file
NEWS	25	Sep 16	Indexing added to some pre-1967 records in CA/CAPLUS
NEWS	26	Sep 16	CA Section Thesaurus available in CAPLUS and CA
NEWS	27	Oct 01	CASREACT Enriched with Reactions from 1907 to 1985
NEWS	28	Oct 21	EVENTLINE has been reloaded
NEWS	29	Oct 24	BEILSTEIN adds new search fields
NEWS	30	Oct 24	Nutraceuticals International (NUTRACEUT) now available on
STN			
NEWS	31	Oct 25	MEDLINE SDI run of October 8, 2002
NEWS	32	Nov 18	DKILIT has been renamed APOLLIT
NEWS	33	Nov 25	More calculated properties added to REGISTRY
NEWS	34	Dec 02	TIBKAT will be removed from STN
NEWS	35	Dec 04	CSA files on STN
NEWS	36	Dec 17	PCTFULL now covers WP/PCT Applications from 1978 to date
NEWS	37	Dec 17	TOXCENTER enhanced with additional content
NEWS	38	Dec 17	Adis Clinical Trials Insight now available on STN
NEWS	39	Dec 30	ISMEC no longer available

NEWS EXPRESS December 31 CURRENT WINDOWS VERSION IS V6.01a,
 CURRENT MACINTOSH VERSION IS V6.0a(ENG) AND V6.0Ja(JP),
 AND CURRENT DISCOVER FILE IS DATED 01 OCTOBER 2002
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* * * * * STN Columbus * * * * *

FILE 'HOME' ENTERED AT 13:52:58 ON 06 JAN 2003

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	ENTRY	SESSION
FULL ESTIMATED COST	0.21	0.21

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=> s liquid (w)droplet(w) aerosol
 L1 11 LIQUID (W) DROPLET(W) AEROSOL

=> duplicate remove
 ENTER L# LIST OR (END):l1
 DUPLICATE PREFERENCE IS 'MEDLINE, CAPLUS, EMBASE, BIOSIS'
 KEEP DUPLICATES FROM MORE THAN ONE FILE? Y/(N):n
 PROCESSING COMPLETED FOR L1
 L2 6 DUPLICATE REMOVE L1 (5 DUPLICATES REMOVED)

=> d l2 1- ibib,abs
 YOU HAVE REQUESTED DATA FROM 6 ANSWERS - CONTINUE? Y/(N):y

L2 ANSWER 1 OF 6 CAPLUS COPYRIGHT 2003 ACS
 ACCESSION NUMBER: 2001:507506 CAPLUS
 DOCUMENT NUMBER: 135:97468
 TITLE: .gamma.-IFN liquid-droplet

aerosol and method
 INVENTOR(S): Emlen, J. Woodruff; Van Vlasselaer, Peter
 PATENT ASSIGNEE(S): Intermune Pharmaceuticals, Inc., USA
 SOURCE: PCT Int. Appl., 29 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001049260	A2	20010712	WO 2000-US42831	20001222
WO 2001049260	A3	20020207		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2001043906	A1	20011122	US 2000-747383	20001222
BR 2000016884	A	20021001	BR 2000-16884	20001222
NO 2002003135	A	20020823	NO 2002-3135	20020627
PRIORITY APPLN. INFO.:			US 1999-173926P	P 19991230
			WO 2000-US42831	W 20001222

AB A liq.-droplet aerosol compn. for delivery
 to a patient's respiratory tract is disclosed. The aerosol is formed by
 placing an aq. .gamma.-IFN soln. having stabilizing and dispersing
 components against a plate having defined-size openings, and forcing the
 soln. through the openings under conditions effective to form aq.
 droplets
 having a vol. mean diam. in one or more of a no. of selected sizes in the
 1-10 .mu. size range. The aerosol has the desired-size droplets and a
 .gamma.-IFN biol. activity and mol. size distribution substantially the
 same as that of the aq. .gamma.-IFN soln. Also disclosed is a method of
 administering to a selected region of a patient's respiratory tract, an
 amt. of human .gamma.-IFN having a known, selected gamma-interferon biol.
 activity and mol. size distribution.

L2 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 1
 ACCESSION NUMBER: 1999:469947 CAPLUS
 DOCUMENT NUMBER: 131:119807
 TITLE: Performance evaluation of the sampling head and
 annular kinetic impactor in the Savannah River Site
 alpha continuous air monitor
 AUTHOR(S): Chen, Bean T.; Hoover, Mark D.; Newton, George J.;
 Montano, Sandra J.; Gregory, Donald S.
 CORPORATE SOURCE: Health Effects Laboratory Division, National
 Institute
 for Occupational Safety and Health, Morgantown, WV,
 26505, USA
 SOURCE: Aerosol Science and Technology (1999), 31(1), 24-38
 CODEN: ASTYDQ; ISSN: 0278-6826
 PUBLISHER: Taylor & Francis
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 AB Evaluation and testing of the Savannah River Site (SRS) impactor-type

alpha continuous air monitor (CAM) to det. device particle delivery and collection efficiency using fluorescence-labeled, polystyrene latex spheres and liq. droplet aerosols is described. Particle sampling efficiency through the dome-shape sampling inlet for particles with aerodynamic diams. of 6.2 and 10 .mu.m was 98%

at

20 cfm (566 L/min), 90% at 32 cfm (906 L/min), and 87% at 40 cfm (1132 L/min) sampling flow rates. Internal delivery efficiency through the CAM was >94% at 20 and 32 cfm for 0.5-, 1.1-, 2.2-, and 3.2-.mu.m particles and >90% for 6.2 .mu.m particles. For 10-.mu.m particles, the internal delivery efficiency was 91% at 20 cfm and decreased to 83% at 32 cfm and 77% at 40 cfm. The 50% cutoff aerodynamic diam. for the impactor was 3.2 .mu.m at 20 cfm, 2.6 .mu.m at 32 cfm, and 2.3 .mu.m at 40 cfm. For a typical radioactive aerosol in the workplace (activity median aerodynamic diam. = 5 .mu.m with a geometric std. deviation of 2), these cutoff

diams.

provided collection efficiencies of 74% at 20 cfm, 83% at 32 cfm, and 87% at 40 cfm. The normal grease layer of 1.5 mg routinely applied to the planchet of the SRS CAM was adequate to quant. retain all collected particles with diams. .ltoreq.3.2 .mu.m at flow rates of 20, 32, and 40 cfm. For particle sizes of 6.2 and 10 .mu.m, .apprx.80-85% of particles were retained on the impactor planchet; 15-20% were re-entrained into the exhaust airstream due to particle bounce. SRS CAM delivery and

collection

efficiencies can be combined to yield overall efficiencies to detect airborne actinide aerosols as a function of particle size. For 6.2 and

10

.mu.m aerodynamic diam. particles, total collection efficiency of the SRS CAM at 20, 32, and 40 cfm exceeded the conservative assumption of 50% efficiency for Pt particle collection traditionally used at SRS.

REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS

FORMAT RECORD. ALL CITATIONS AVAILABLE IN THE RE

L2 ANSWER 3 OF 6 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1998:372271 CAPLUS

DOCUMENT NUMBER: 129:117091

TITLE: Sampling and conditioning of gas containing liquids in

droplet or aerosol form

AUTHOR(S): Mayeaux, Donald P.

CORPORATE SOURCE: A+ Corporation, Prairieville, LA, 70769, USA

SOURCE: Proceedings of the Annual ISA Analysis Division Symposium (1998), 31, 129-137
CODEN: ANDIEY; ISSN: 1050-6527

PUBLISHER: Instrument Society of America

DOCUMENT TYPE: Journal

LANGUAGE: English

AB This presentation addresses problems assocd. with sampling gas which contains liq. in droplet or aerosol form. By elimination of entrained liq. at prevailing process conditions, gas compn. changes are avoided. Techniques to prevent condensation from occurring after the gas sample is extd. are also discussed.

L2 ANSWER 4 OF 6 MEDLINE

DUPLICATE 2

ACCESSION NUMBER: 92209411 MEDLINE

DOCUMENT NUMBER: 92209411 PubMed ID: 1555522

TITLE: Two-week aerosol inhalation study in rats of ethylene oxide/propylene oxide copolymers.

COMMENT: Erratum in: Drug Chem Toxicol 1992;15(3):269-70
AUTHOR: Ulrich C E; Geil R G; Tyler T R; Kennedy G L Jr; Birnbaum
H

CORPORATE SOURCE: A
International Research and Development Corporation,
Mattawan, MI 49071.

SOURCE: DRUG AND CHEMICAL TOXICOLOGY, (1992) 15 (1) 15-31.
Journal code: 7801723. ISSN: 0148-0545.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199205

ENTRY DATE: Entered STN: 19920515

Last Updated on STN: 19920515

Entered Medline: 19920504

AB Previous studies have shown that aerosols of an ethylene oxide/propylene
oxide copolymer (UCON 50-HB-5100) produced an inflammatory response in
lungs of rats in short-term repeated exposures at relatively low
concentrations. This study was carried out on related polyalkylene
glycols

(EO/PO copolymers) to determine if similar effects would occur upon
short-term repeated exposure. Rats were treated by whole body
liquid droplet aerosol exposures of six hours
per day, five days per week for two consecutive weeks to each of five
EO/PO copolymers. The exposure level for the positive control (UCON
50-HB-5100) was 55 mg/m³, while the remaining 4 test copolymers were
evaluated at 100 mg/m³. Each exposure group consisted of ten male albino
rats. After three exposures, nine of ten rats exposed to UCON 50-HB-5100,
and six of ten rats exposed to UCON 50-HB-2000 had died. At necropsy,
congestion, consolidation and red discoloration of the lungs were noted.

A moderate to severe alveolitis, characterized by intraalveolar edema,
hemorrhage and fibrin deposition, was observed after five days of
exposure. At necropsy, these rats exhibited elevated lung weights and
similar macroscopic and microscopic lesions. Rats exposed to the other
test materials (UCON 75-H-1400, Pluronic L17R1, Pluronic L31, and

Pluronic
L64) survived with essentially no signs of toxicity through the ten
exposure days. Body weights, organ weights, hematological evaluation,
pharmacotoxic signs, and macroscopic and microscopic evaluation after
necropsy were similar between groups and when compared to the negative
control group. Only a slight alveolitis was noted after two weeks of
exposure which subsided by two-weeks post exposure.

L2 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1987:69552 CAPLUS

DOCUMENT NUMBER: 106:69552

TITLE: The behavior of **liquid droplet
aerosols** in an APS 3300

AUTHOR(S): Griffiths, W. D.; Iles, P. J.; Vaughan, N. P.

CORPORATE SOURCE: Occup. Med. Hyg. Lab., Health Saf. Exec., London, NW2
6LN, UK

SOURCE: Journal of Aerosol Science (1986), 17(6), 921-30

CODEN: JALSB7; ISSN: 0021-8502

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Monodisperse liq. and solid polystyrene latex (PSL) aerosols behaved in a
significantly different manner in an Aerodynamic Particle Sizer (APS)
3300. The results were compared with those of other recent
investigations

with a fair degree of agreement. The APS measurements indicated a decrease of the expected aerodynamic diam. of all of the liq. aerosols tested. This decrease might be dependent on the viscosity and diam. on generation of the drop. Monodisperse PSL should be used to calibrate the APS throughout its operating range, instead of a liq. aerosol.

L2 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1977:489845 CAPLUS

DOCUMENT NUMBER: 87:89845

TITLE: Critical review of the USCG report by Raj et al
(1974)

on spills of liquid anhydrous ammonia on to water,
with an alternative assessment of the experimental
results

AUTHOR(S): Griffiths, R. F.

CORPORATE SOURCE: Saf. Reliability Dir., UKAEA, Culcheth/Warrington, UK

SOURCE: U. K. At. Energy Auth., Saf. Reliab. Dir., [Rep.] SRD
(1977), SRD R 67, 17 pp.

CODEN: UKSRAP

DOCUMENT TYPE: Report

LANGUAGE: English

AB A polemic. the P. K. Raj (1974) report (NTIS AD 779400) concerning liq.
NH3 spills from refrigerated storage tanks and the release of NH3 from
them as a pure undild. vapor is challenged on the grounds that it is
incompatible with exptl. measurements. NH3 is released as a plume contg.
both vapor and liq. droplet aerosol, by
virtue of which it is rendered nonbuoyant.

=> s lung (w)delivery (w) cytokines

L3 0 LUNG (W) DELIVERY (W) CYTOKINES

=> s lung (s) delivery (s) cytokines

L4 259 LUNG (S) DELIVERY (S) CYTOKINES

=> s aerosol (s) composition

L5 8004 AEROSOL (S) COMPOSITION

=> s l4 and l5

L6 0 L4 AND L5

=> s aerosol

L7 127142 AEROSOL

=> s l4 and l7

L8 42 L4 AND L7

=> duplicate remove l8

DUPLICATE PREFERENCE IS 'MEDLINE, CAPLUS, CANCERLIT, EMBASE, BIOSIS'

KEEP DUPLICATES FROM MORE THAN ONE FILE? Y/(N):n

PROCESSING COMPLETED FOR L8

L9 17 DUPLICATE REMOVE L8 (25 DUPLICATES REMOVED)

=> d l9 1- ibib,abs

YOU HAVE REQUESTED DATA FROM 17 ANSWERS - CONTINUE? Y/(N):y

L9 ANSWER 1 OF 17 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:71808 CAPLUS

DOCUMENT NUMBER: 136:123657

TITLE: Modulated release particles for drug delivery to
lungs

INVENTOR(S): Adjai, Akwete L.; Zhu, Yaping; Cutie, Anthony J.;
Sun,
John Z.
PATENT ASSIGNEE(S): Aeropharm Technology Incorporated, USA
SOURCE: PCT Int. Appl., 29 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002005730	A1	20020124	WO 2001-US41120	20010625
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
PRIORITY APPLN. INFO.:			US 2000-219051P	P 20000718
			US 2000-702894	A 20001031
AB A polymeric construct is disclosed. The construct comprises a biodegradable ABA block copolymer (e.g., polyglycolide-poly lactide) having a selected drug assocd. therewith. The drug thus present is provided in a slow release form. Thus, a polymer was obtained from polyglycolide-poly lactide with PEG as the crosslinker. The particle size distribution anal. of the amylin-polymer compn. was detd.				
REFERENCE COUNT:	2	THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE		
FORMAT				

L9 ANSWER 2 OF 17 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:616197 CAPLUS
DOCUMENT NUMBER: 137:174934
TITLE: Modulated-release polysaccharide aerosol particles for lung delivery
INVENTOR(S): Zhu, Yaping; Stefanos, Simon G.; Kline, Lukeysa; Adjai, Akwete L.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 9 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002110539	A1	20020815	US 2001-784670	20010215
WO 2002066077	A2	20020829	WO 2002-US3970	20020206
WO 2002066077	A3	20021024		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,				

LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
 PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,
 UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
 RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,
 CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,
 BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2001-784670 A 20010215

AB A polymeric construct for lung delivery comprises a polysaccharide vehicle

entrapping a selected medicament. A polysaccharide is present in an amt. of about 0.0000001-10% by wt. of the construct and it is selected from, e.g., alginic acid, various gums, cellulose, agar, carrageenan, gelatin, galacturonic acid, etc. The medicament entrapped within the construct is provided in a slow release form. The medicament is for example a protein or peptide having a mol. size of about 1-150 kD, selected from insulin, glucagon, LH-RH, daltirex, leuprolide, calcitonin, parathyroid hormone, TRH, growth hormone-releasing hormone, G-CSF, a cytokine, DNase, heparin, an oligonucleotide, a monoclonal antibody, a vaccine, etc. Depending

upon

the concn. of the polymer drug release rates range from 5 min to several hours.

L9 ANSWER 3 OF 17 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:616192 CAPLUS

DOCUMENT NUMBER: 137:159362

TITLE: Modulated-release polymeric silicate particles for lung delivery

INVENTOR(S): Zhu, Yaping; Adjei, Akwete L.

PATENT ASSIGNEE(S): USA

SOURCE: U.S. Pat. Appl. Publ., 11 pp.

CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002110527	A1	20020815	US 2001-784671	20010215
US 6485707	B2	20021126		
WO 2002066009	A1	20020829	WO 2002-US3995	20020207
WO 2002066009	C2	20021205		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
 CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
 GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
 LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
 PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,
 UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
 RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,
 CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,
 BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2001-784671 A 20010215

AB A modulated-release aerosol formulation for lung delivery comprises a polymeric silicate construct, e.g., silica gel or fumed silica

gel, having a selected medicament assocd. there with, and a fluid carrier for carrying and delivering the construct. The polymer is present in an amt. of about 0.000001-10% of the total wt. of the formulation. A medicament comprises a protein or peptide with a mol. size of about 1-150 kD, such as insulin, amylin, an interleukin, an interferon, heparin, a

thrombolytic, an antitrypsin, a hormone, a growth factor, an enzyme, etc.

L9 ANSWER 4 OF 17 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:616191 CAPLUS

DOCUMENT NUMBER: 137:174932

TITLE: Modulated-release polysaccharide particles for lung delivery

INVENTOR(S): Zhu, Yaping; Stefanos, Simon G.; Kline, Lukeysa; Adjei, Akwete L.

PATENT ASSIGNEE(S): USA

SOURCE: U.S. Pat. Appl. Publ., 10 pp.

CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002110526	A1	20020815	US 2001-784566	20010215
US 6475468	B2	20021105		
WO 2002066078	A2	20020829	WO 2002-US3971	20020206
WO 2002066078	A3	20021024		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2001-784566 A 20010215

AB A modulated (slow) release **aerosol** formulation comprises a particulate polysaccharide polymer, e.g., alginic acid, various gums, cellulose, gelatin, agar, carrageenan, gelatin, etc., having a selected medicament assocd. there with, and a fluid carrier for carrying and delivering the construct. The polymer is present in an amt. of about 0.000001-10% of the total wt. of the formulation. A medicament is, for example, a protein or peptide drug, such as insulin, amylin, glucagon, LH-RH, deltirex, leuprolide, gosorelin, nafarelin, octreotide, somatostatin, calcitonin, etc. A fluid carrier is selected from a propellant, air, carbon dioxide, nitrogen or a hydrocarbon. The **aerosol** is dispensed in a canister equipped with a metered dose valve.

L9 ANSWER 5 OF 17 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:616190 CAPLUS

DOCUMENT NUMBER: 137:174931

TITLE: Modulated release particles for pharmaceutical lung delivery

INVENTOR(S): Adjei, Akwete L.; Zhu, Yaping

PATENT ASSIGNEE(S): USA

SOURCE: U.S. Pat. Appl. Publ., 11 pp.

CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002110525	A1	20020815	US 2001-784556	20010215
WO 2002066008	A1	20020829	WO 2002-US3992	20020207

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2001-784556 A 20010215

OTHER SOURCE(S): MARPAT 137:174931

AB A modulated release **aerosol** formulation is disclosed. The formulation comprises a polysaccharide polymer having a selected drug assocd., a fluid carrier for carrying and delivering the construct and a stabilizer. The stabilizer is selected from the group consisting of an amino acid e.g., a monoaminocarboxylic acid, a monoaminodicarboxylic acid and a diaminomonomocarboxylic acid. The polysaccharide can be from alginic acid or a salt, e.g., guar gum, gum karaya, agar, carrageenan, and cellulose.

L9 ANSWER 6 OF 17 MEDLINE DUPLICATE 1

ACCESSION NUMBER: 2002696539 IN-PROCESS

DOCUMENT NUMBER: 22345302 PubMed ID: 12458152

TITLE: Pharmacological approaches for the discovery and development of new anti-inflammatory agents for the treatment of cystic fibrosis.

AUTHOR: Konstan Michael W; Davis Pamela B

CORPORATE SOURCE: Department of Pediatrics, Case Western Reserve University School of Medicine and Rainbow Babies and Children's Hospital, 11100 Euclid Avenue, 44106, Cleveland, OH, USA.

SOURCE: Adv Drug Deliv Rev, (2002 Dec 5) 54 (11) 1409-23. Journal code: 8710523. ISSN: 0169-409X.

PUB. COUNTRY: Netherlands

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals

ENTRY DATE: Entered STN: 20021217

Last Updated on STN: 20021217

AB Some of the most important pathobiology in cystic fibrosis occurs not as a

direct result of impaired chloride transport, but the downstream consequences of defective CFTR function, particularly the **lung** infection and inflammation that ultimately takes the lives of most patients. Interrupting the vicious cycle of infection and inflammation is effective in slowing the course of the disease, and antibiotics have long been the staple of pulmonary therapy. However, limiting the inflammatory response in the CF **lung** is also effective. High dose ibuprofen clearly retards progression of **lung** disease, but also entrains adverse events that mar its therapeutic utility, so alternative anti-inflammatory agents are necessary. Because of the remarkable therapeutic success of ibuprofen, consideration should be given to finding

less toxic alternatives. However, it is also appropriate to consider the mechanisms by which the inflammatory response occurs in the CF **lung**, and identify sites to interrupt it. Sites at which therapeutic intervention is possible are the neutralization of

cytokines such as tumor necrosis factor-alpha, interleukin (IL)-1beta, or IL-8 with specific antibodies or receptor antagonists, inhibition of the intracellular signaling cascades that result in cytokine production (for example, at the level of p38 MAP kinase), application of cytokines such as IL-10 that are themselves anti-inflammatory, or modulating the arachidonic acid cascade with inhibitors directed at leukotriene B(4). In addition, interventions designed to limit the consequences of the inflammatory response, such as protease inhibitors and reagents to limit the ill effects of DNA accumulation in airways, are in use. To limit adverse effect and concentrate the therapeutic effect, there may be value in targeting **delivery** of the therapeutic reagents to the inflamed site, either by specifically directing systemic **delivery** or by exploitation of the **aerosol** route. Treating the inflammatory response is important, for the data from the ibuprofen study show that the effects of anti-inflammatory therapy are additive or even synergistic with intensive conventional therapy and alter the rate of decline of pulmonary function, and therefore benefits for survival of patients with CF are to be expected.

L9 ANSWER 7 OF 17 MEDLINE DUPLICATE 2
 ACCESSION NUMBER: 2001245334 MEDLINE
 DOCUMENT NUMBER: 21101774 PubMed ID: 11181627
 TITLE: Methodology for the measurement of mucociliary function in the mouse by scintigraphy.
 AUTHOR: Foster W M; Walters D M; Longphre M; Macri K; Miller L M
 CORPORATE SOURCE: Department of Pulmonary and Critical Care Medicine, Duke University Medical Center, Durham, North Carolina 27710, USA.
 CONTRACT NUMBER: ES-03810 (NIEHS)
 HL-62641 (NHLBI)
 SOURCE: JOURNAL OF APPLIED PHYSIOLOGY, (2001 Mar) 90 (3) 1111-7.
 Journal code: 8502536. ISSN: 8750-7587.
 PUB. COUNTRY: United States
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200105
 ENTRY DATE: Entered STN: 20010517
 Last Updated on STN: 20010517
 Entered Medline: 20010510

AB The objective of the study was to develop a scintigraphic method for measurement of airway mucociliary clearance in small laboratory rodents such as the mouse. Previous investigations have characterized the secretory cell types present in the mouse airway, but analysis of the mucus transport system has been limited to in vitro examination of tissue explants or invasive in vivo measures of a single airway, the trachea. Three methods were used to deposit insoluble, radioisotopic colloidal particles: oropharyngeal aspiration, intratracheal instillation, and nose-only **aerosol** inhalation. The initial distribution of particles within the lower respiratory tract was visualized by gamma-camera, and clearance of particles was followed intermittently over 6 h and at the conclusion, 24 h postdelivery. Subsets of mice underwent lavage for evidence of tissue inflammation, and others were restudied for reproducibility of the methods. The aspiration and instillation methods of **delivery** led to greater distributions of deposited activity within

the **lungs**, i.e., approximately 60--80% of the total respiratory tract radioactivity, whereas the nose-only **aerosol** technique attained a distribution of 32% to the **lungs**. However, the **aerosol** technique maximized the fraction of particles that cleared the airway over a 24-h period, i.e, deposited onto airway epithelial surfaces and cleared by mucociliary function such that **lung** retention at 24 h averaged 57% for **delivery** by **aerosol** inhalation and > or =80% for the aspiration or intratracheal instillation techniques. Particle **delivery** methods did not cause **lung** inflammation/injury with use of inflammatory cells and chemoattractant **cytokines** as criteria. Scintigraphy can discern particle deposition and clearance from the lower respiratory tract in the mouse,

is

noninvasive and reproducible, and includes the capability for restudy and **lung** lavage when time course or chronic treatments are being considered.

L9 ANSWER 8 OF 17 MEDLINE DUPLICATE 3
 ACCESSION NUMBER: 2001257717 MEDLINE
 DOCUMENT NUMBER: 21214768 PubMed ID: 11313798
 TITLE: Pulmonary cytokine responses associated with PEI-DNA **aerosol** gene therapy.
 AUTHOR: Gautam A; Densmore C L; Waldrep J C
 CORPORATE SOURCE: Department of Molecular Physiology and Biophysics, Baylor College of Medicine, 1 Baylor Plaza, Houston, TX 77030, USA.
 SOURCE: GENE THERAPY, (2001 Feb) 8 (3) 254-7.
 Journal code: 9421525. ISSN: 0969-7128.
 PUB. COUNTRY: England: United Kingdom
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200105
 ENTRY DATE: Entered STN: 20010521
 Last Updated on STN: 20010521
 Entered Medline: 20010517

AB Pulmonary gene therapy with nonviral vectors delivered by instillation or intravenously has typically been associated with co-induction of cytokine responses attributed to the CpG motifs in the bacterial plasmid. Alternative **delivery** systems are being developed to circumvent the cytokine responses to the plasmid. **Aerosol delivery** of polyethylenimine--DNA (PEI-DNA) complexes leads to localized, high levels of transgene expression in the **lungs**. In this study, we show that PEI-DNA **aerosol delivery** is also associated with induction of tumor necrosis factor alpha (TNF-alpha) and interleukin 1 beta (IL-1 beta) in the **lung** and bronchoalveolar lavage fluid (BALF). However, there is no increase in the serum levels of these **cytokines**. The levels of these **cytokines** peak at 5--8 h after **aerosol** exposure for **lung** tissue, and at 24 h for BALF. However, the levels detected are much lower than those observed when PEI-DNA complexes, guanidinium--cholesterol: dioleoylphosphatidyl--ethanolamine liposome--DNA (BGTC:DOPE--DNA) complexes or 1,2-dioleoyl-sn-glycero-3-trimethylammonium--propane--cholesterol:DNA (DOTAP-Chol:DNA) complexes were delivered intravenously. Also, the **lung** cytokine levels were higher when BGTC:DOPE--DNA complexes were delivered by **aerosol** to the mice. Although the mechanism remains to be elucidated, the data suggest that **aerosol** exposure to PEI--DNA complexes can achieve high levels of transgene expression in the **lungs** without inducing high levels of cytokine responses.

L9 ANSWER 9 OF 17 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2000:756484 CAPLUS

DOCUMENT NUMBER: 133:329593

TITLE: Low adenosine anti-sense oligonucleotide, compositions, kit and method for treatment of airway disorders associated with bronchoconstriction, lung inflammation, allergy(ies) and surfactant depletion

INVENTOR(S): Nyce, Jonathan W.

PATENT ASSIGNEE(S): East Carolina University, USA

SOURCE: PCT Int. Appl., 1592 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000062736	A2	20001026	WO 2000-US8020	20000324
WO 2000062736	A3	20011011		

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

BR 2000006019	A	20010313	BR 2000-6019	20000324
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EP 1168919	A2	20020109	EP 2000-919668	20000324
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R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO

PRIORITY APPLN. INFO.:

US 1999-127958P P 19990406

WO 2000-US8020 W 20000324

OTHER SOURCE(S): MARPAT 133:329593

AB An in vivo method of selectively delivering a nucleic acid to a target gene or mRNA, comprises the topical administration, e.g. to the respiratory system, of a subject of a therapeutic amt. of an oligonucleotide (oligo) that is antisense to the initiation codon region, the coding region, the 5' or 3' intron-exon junctions or regions within 2 to 10 nucleotides of the junctions of the gene or antisense to a mRNA complementary to the gene in an amt. effective to reach the target polynucleotide and reducing or inhibiting expression. In addn. a method of treating an adenosine-mediated effect comprises topically administering

to a subject an antisense oligo in an amt. effective to treat the respiratory, pulmonary, or airway disease. In order to minimize triggering adenosine receptors by their metab., the administered oligos have a low content of or are essentially free of adenosine. A pharmaceutical compn. and formulations comprise the oligo antisense to an adenosine receptor, genes and mRNAs encoding them, genomic and mRNA flanking regions, intron and exon borders and all regulatory and functionally related segments of the genes and mRNAs encoding the polypeptides, their salts and mixts. Various formulations contain a requisite carrier, and optionally other additives and biol. active agents.

The low-adenosine or adenosine-free (des-A) agent for practicing the method of the invention may be prepd. by selecting a target gene(s), genomic flanking region(s), RNA(s) and/or polypeptide(s) assocd. with a

disease(s) or condition(s) afflicting lung airways, obtaining the sequence of the mRNA(s) corresponding to the target gene(s) and/or genomic flanking region(s), and/or RNAs encoding the target polypeptide(s), selecting at least one segment of the mRNA which may be up to 60 % free of thymidine (T) and synthesizing one or more anti-sense oligonucleotide(s) to the mRNA segments which are free of adenosine (A) by substituting a universal base for A when present in the oligonucleotide. The agent may be prepd. by selection of target nucleic acid sequences with GC running stretches, which have low T content, and by optionally replacing A in the antisense oligonucleotides with a "Universal or alternative base". The agent, compn. and formulations are used for prophylactic, preventive and therapeutic treatment of ailments assocd. with impaired respiration, lung allergy(ies) and/or inflammation and depletion lung surfactant or surfactant hypoprodn., such as pulmonary vasoconstriction, inflammation, allergies, allergic rhinitis, asthma, impeded respiration, lung pain, cystic fibrosis, bronchoconstriction. The present treatment is suitable for administration in combination with other treatments, e.g. before, during and after other treatments, including radiation, chemotherapy, antibody therapy and surgery, among others. Alternatively, the present agent is effectively administered prophylactically or therapeutically by itself for conditions without known therapies or as a substitute for therapies exhibiting undesirable side effects. The treatment of this invention may be administered directly into the respiratory system of a subject so that the agent has direct access to the lungs, or by other effective routes of administration, e.g. topically, transdermally, by implantation, etc., in an amt. effective to reduce or inhibit the symptoms of the ailment.

L9 ANSWER 10 OF 17 MEDLINE DUPLICATE 4
 ACCESSION NUMBER: 2000392744 MEDLINE
 DOCUMENT NUMBER: 20308150 PubMed ID: 10848908
 TITLE: Influence of bronchial allergen challenge on histamine release by human basophils.
 AUTHOR: Lie W J; Van Der Veen M J; Knol E F; Mul F P; Jansen H M; Roos D; Van Der Zee J S
 CORPORATE SOURCE: Central Laboratory of The Netherlands Red Cross Blood Transfusion Service and the Laboratory for Experimental and Clinical and Immunology, Academic Medical Center, University of Amsterdam, The Netherlands.
 SOURCE: CLINICAL AND EXPERIMENTAL ALLERGY, (2000 Jun) 30 (6) 882-90.
 Journal code: 8906443. ISSN: 0954-7894.
 PUB. COUNTRY: ENGLAND: United Kingdom
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200008
 ENTRY DATE: Entered STN: 20000824
 Last Updated on STN: 20000824
 Entered Medline: 20000817
 AB BACKGROUND: Basophils can be primed by **cytokines** such as interleukin (IL) -3, IL-5 or granulocyte macrophage-colony stimulating factor (GM-CSF). It has been described that the concentrations of these **cytokines** are enhanced at sites of allergic inflammation as well as systemic in allergic asthma. OBJECTIVE: To investigate the priming

status of basophils as detected by thapsigargin-induced histamine release during bronchial allergen challenge. METHODS: Ten subjects allergic to house dust mite were challenged via an **aerosol delivery** system. Spontaneous leucocyte histamine release as well as histamine release induced by various stimuli was measured in vitro at several time points. In addition, **lung** function parameters, serum IL-5 and blood eosinophil counts were evaluated. RESULTS: We found no effect of bronchial allergen challenge upon spontaneous leucocyte histamine release,

nor upon histamine release induced by anti-immunoglobulin (Ig) E, house dust mite extract, C5a, fMLP, IL-3, PMA+ thapsigargin or IL-3+ thapsigargin. However, the priming status of basophils as measured by thapsigargin-induced histamine release was enhanced at 24 h after bronchial allergen challenge. Analysis of the individual data showed a heterogeneous initial response (30 min, 6 h) followed by a predominant increase at 24 h after allergen challenge. This increase in the thapsigargin-induced histamine release correlated with the increase in serum IL-5 levels at 24 h after allergen challenge. CONCLUSION: The priming status of human basophils as measured by thapsigargin-induced histamine release is enhanced 24 h after allergen challenge.

L9 ANSWER 11 OF 17 MEDLINE DUPLICATE 5
 ACCESSION NUMBER: 1999394500 MEDLINE
 DOCUMENT NUMBER: 99394500 PubMed ID: 10466624
 TITLE: Systemic and local interferon gamma gene delivery to the lungs for treatment of allergen-induced airway hyperresponsiveness in mice.
 AUTHOR: Dow S W; Schwarze J; Heath T D; Potter T A; Gelfand E W
 CORPORATE SOURCE: Department of Medicine, National Jewish Medical and Research Center, Denver, CO 80206, USA.
 CONTRACT NUMBER: AI-37905 (NIAID)
 HL-36577 (NHLBI)
 SOURCE: HUMAN GENE THERAPY, (1999 Aug 10) 10 (12) 1905-14.
 Journal code: 9008950. ISSN: 1043-0342.
 PUB. COUNTRY: United States
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 199912
 ENTRY DATE: Entered STN: 20000113
 Last Updated on STN: 20000113
 Entered Medline: 19991207

AB Allergen-induced airway hyperresponsiveness, an animal model of asthma in humans, may respond to immunotherapy with Th1 **cytokines**. For example, local administration of recombinant IL-12 or IFN-gamma, or intratracheal **delivery** of the genes for these **cytokines**, has been shown to reduce the severity of allergen-induced airway hyperresponsiveness (AHR) in rodent models. We reasoned that systemic cytokine gene **delivery** to the **lungs** by intravenous injection of lipid-DNA complexes might also be an effective approach to treatment of allergen-induced AHR. Therefore, the effects of either systemic or local pulmonary IFN-gamma gene **delivery** were evaluated in mice with allergen-induced AHR. The effects of treatment on AHR, airway eosinophilia and cytokine production, and serum IgE concentrations were evaluated in mice that were first sensitized to ovalbumin and then subjected to **aerosol** ovalbumin challenge. Intravenous IFN-gamma gene **delivery** significantly inhibited development of AHR and airway eosinophilia and decreased serum IgE levels,
 compared with control mice or mice treated with noncoding DNA.

Intratracheal IFN-gamma gene **delivery** also significantly inhibited AHR and airway eosinophilia, but did not affect serum IgE levels. Treatment with recombinant IFN-gamma was much less effective than IFN-gamma gene **delivery** by either route. We conclude that either systemic or local pulmonary **delivery** of a Th1 cytokine gene such as IFN-gamma may be an effective approach for treatment of allergen-induced asthma.

L9 ANSWER 12 OF 17 MEDLINE DUPLICATE 6
 ACCESSION NUMBER: 1998099769 MEDLINE
 DOCUMENT NUMBER: 98099769 PubMed ID: 9435302
 TITLE: IL-6 is an antiinflammatory cytokine required for
 controlling local or systemic acute inflammatory
 responses.
 AUTHOR: Xing Z; Gauldie J; Cox G; Baumann H; Jordana M; Lei X F;
 Achong M K
 CORPORATE SOURCE: Immunology and Infection Program, Department of Pathology,
 McMaster University, Hamilton, Ontario, L8N 3Z5 Canada..
 xingz@fhs.csu.mcmaster.ca
 SOURCE: JOURNAL OF CLINICAL INVESTIGATION, (1998 Jan 15) 101 (2)
 311-20.
 Journal code: 7802877. ISSN: 0021-9738.
 PUB. COUNTRY: United States
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
 ENTRY MONTH: 199802
 ENTRY DATE: Entered STN: 19980217
 Last Updated on STN: 19980217
 Entered Medline: 19980205
 AB IL-6 is induced often together with the proinflammatory **cytokines**
 TNFalpha and IL-1 in many alarm conditions, and circulating IL-6 plays an
 important role in the induction of acute phase reactions. However,
 whether
 this endogenous IL-6 plays any additional pro- or antiinflammatory roles
 in local or systemic responses remains unclear. In this study, the role
 of
 IL-6 in acute inflammatory responses was investigated in animal models of
 endotoxic **lung** or endotoxemia by using IL-6+/+ and IL-6-/- mice.
Aerosol exposure of endotoxin induced increased IL-6 and
 proinflammatory **cytokines** TNFalpha and MIP-2 and a neutrophilic
 response in the **lung** of IL-6+/+ mice. However, the levels of
 TNFalpha and MIP-2 and neutrophilia were significantly higher in the
lung of IL-6-/- mice. The rate of neutrophil apoptosis in these
 mice was similar to that in IL-6+/+ mice. A low constitutive level of
 antiinflammatory cytokine IL-10 was not enhanced by endotoxin and
 remained
 similar in the **lung** in both IL-6+/+ and IL-6-/- mice.
 Systemically, intraperitoneal **delivery** of endotoxin resulted in
 much more pronounced circulating levels of TNFalpha, MIP-2, GM-CSF, and
 IFNgamma in IL-6-/- mice than in IL-6+/+ mice, and administration of
 recombinant IL-6 to IL-6-/- mice abolished these differences. In
 contrast,
 circulating IL-10 levels were induced to a similar degree in both IL-6+/+
 and IL-6-/- mice. Thus, our studies reveal that endogenous IL-6 plays a
 crucial antiinflammatory role in both local and systemic acute
 inflammatory responses by controlling the level of proinflammatory, but
 not antiinflammatory, **cytokines**, and that these antiinflammatory
 activities by IL-6 cannot be compensated for by IL-10 or other IL-6
 family

members.

L9 ANSWER 13 OF 17 MEDLINE DUPLICATE 7
ACCESSION NUMBER: 1998382063 MEDLINE
DOCUMENT NUMBER: 98382063 PubMed ID: 9717963
TITLE: Compartmentalized transgene expression of
granulocyte-macrophage colony-stimulating factor (GM-CSF)
in mouse lung enhances allergic airways inflammation.
AUTHOR: Lei X F; Ohkawara Y; Stampfli M R; Gauldie J; Croitoru K;
Jordana M; Xing Z
CORPORATE SOURCE: Department of Pathology, McMaster University, Hamilton,
Ontario, Canada.
SOURCE: CLINICAL AND EXPERIMENTAL IMMUNOLOGY, (1998 Aug) 113 (2)
157-65.
Journal code: 0057202. ISSN: 0009-9104.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199809
ENTRY DATE: Entered STN: 19980917
Last Updated on STN: 19980917
Entered Medline: 19980909
AB To investigate the role of GM-CSF in asthmatic airways inflammation, we
have targeted GM-CSF transgene to the airway cells in a mouse model of
ovalbumin (OVA)-induced allergic airways inflammation, a model in which
there is marked induction of endogenous IL-5 and IL-4 but not GM-CSF.
Following intranasal **delivery** of a replication-deficient
adenoviral gene transfer vector (Ad), transgene expression was found
localized primarily to the respiratory epithelial cells. Intranasal
delivery of 0.03×10^9 plaque-forming units (PFU) of AdGM-CSF
into naive BALB/c mice resulted in prolonged and compartmentalized
release
of GM-CSF transgene protein with a peak concentration of approximately 80
pg/ml detected in bronchoalveolar lavage fluid (BALF) at day 7, but
little
in serum. These levels of local GM-CSF expression per se resulted in no
eosinophilia and only a minimum of tissue inflammatory responses in the
lung of naive mice, similar to those induced by the control
vector. However, such GM-CSF expression in the airways of OVA-sensitized
mice resulted in a much greater and sustained accumulation of various
inflammatory cell types, most noticeably eosinophils, both in BALF and
airway tissues for 15-21 days post-OVA **aerosol** challenge, at
which times airways inflammation had largely resolved in control mice.
While the levels of IL-5 and IL-4 in BALF and the rate of eosinophil
apoptosis were found similar between different treatments, there was an
increased number of proliferative leucocytes in the **lung**
receiving GM-CSF gene transfer. Our results thus provide direct
experimental evidence that GM-CSF can significantly contribute to the
development of allergic airways inflammation through potentiating and
prolonging inflammatory infiltration induced by **cytokines** such
as IL-5 and IL-4.

L9 ANSWER 14 OF 17 MEDLINE DUPLICATE 8
ACCESSION NUMBER: 1998112872 MEDLINE
DOCUMENT NUMBER: 98112872 PubMed ID: 9451042
TITLE: **Aerosol** cyclosporine prevents acute allograft
rejection in experimental lung transplantation.
AUTHOR: Mitruka S N; Pham S M; Zeevi A; Li S; Cai J; Burckart G J;
Yousem S A; Keenan R J; Griffith B P

CORPORATE SOURCE: Department of Cardiothoracic Surgery, University of
Pittsburgh School of Medicine, PA 15261, USA.
CONTRACT NUMBER: RO1-HL48091-03 (NHLBI)
SOURCE: JOURNAL OF THORACIC AND CARDIOVASCULAR SURGERY, (1998 Jan)
115 (1) 28-36; discussion 36-7.
Journal code: 0376343. ISSN: 0022-5223.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199802
ENTRY DATE: Entered STN: 19980226
Last Updated on STN: 19980226
Entered Medline: 19980218

AB BACKGROUND: The incidence of acute rejection and the morbidity of
systemic

cyclosporine (INN: cyclosporine) after **lung** transplantation is
significant. Experimental evidence suggests that the allograft locally
modulates the immune mechanisms of acute rejection. The purpose of this
study was to determine whether aerosolized cyclosporine would prevent
acute cellular rejection, achieve effective graft concentrations with low
systemic drug **delivery**, and locally affect production of the
inflammatory **cytokines** involved in acute rejection. METHODS:
Unilateral orthotopic left **lung** transplantation was performed in
64 rats (ACI to Lewis), which were divided into eight groups (each group,
n = 8): group A, no treatment; groups B to D, **aerosol**
cyclosporine 1 to 3 mg/kg per day, respectively; group E to H, systemic
cyclosporine 2, 5, 10, and 15 mg/kg per day, respectively. After the
animals were killed on postoperative day 2, 4, or 6, the transplanted
lung, native **lung**, spleen, and blood were collected.
Histologic studies, high-pressure liquid chromatography for trough
cyclosporine concentrations, and reverse-transcriptase polymerase chain
reaction for cytokine gene expression were performed. RESULTS: Untreated
animals showed grade 4 rejection by postoperative day 6. **Aerosol**
cyclosporine prevented acute rejection in a dose-dependent fashion, with
group D animals (3 mg/kg per day) showing minimal grade 1 changes. Among
animals receiving systemic cyclosporine, only group H (15 mg/kg per day)
controlled (grade 1) rejection. However, **aerosol** cyclosporine,
at an 80% lower dose, achieved significantly lower concentrations of
cyclosporine in the graft (12,349 vs 28,714 ng/mg, p = 0.002004) and
blood

(725 vs 3306 ng/ml, p = 0.000378). Group F (systemic 5 mg/kg per day) had
higher cyclosporine concentrations in the blood than group D (p =
0.004572) and similar tissue concentrations (p = 0.115180), yet had grade
2 rejection. Reverse-transcriptase polymerase chain reaction demonstrated
equivalent suppression of inducible nitric oxide synthase but a 20- to
25-fold higher expression of interleukin-6, interleukin-10, and
interferon-gamma in group D versus group H recipient allografts.
CONCLUSION: Local **delivery** of cyclosporine by **aerosol**
inhalation dose-dependently prevented acute pulmonary allograft
rejection.

Effective graft levels and low systemic drug **delivery** required
significantly lower doses than systemic therapy alone. The gene
expression
of proinflammatory **cytokines** involved in allograft rejection was
suppressed by **aerosol** cyclosporine therapy.

L9 ANSWER 15 OF 17 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1993:132147 CAPLUS
DOCUMENT NUMBER: 118:132147

TITLE: **Aerosols** for delivery of proteins
 INVENTOR(S): Lohmann, Helmut; Pollmann, Wolfgang; Schneckert, Kurt;
 Zierenberg, Bernd
 PATENT ASSIGNEE(S): Boehringer Ingelheim KG, Germany
 SOURCE: Ger. Offen., 3 pp.
 CODEN: GWXXBX
 DOCUMENT TYPE: Patent
 LANGUAGE: German
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 4117078	A1	19921126	DE 1991-4117078	19910525
WO 9221332	A1	19921210	WO 1992-EP1080	19920516
W: AT, AU, BG, BR, CA, CH, CS, DE, DK, ES, FI, GB, HU, JP, KR, LU, NL, NO, PL, RO, RU, SE, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, MC, NL, SE				
AU 9217557	A1	19930108	AU 1992-17557	19920516
PRIORITY APPLN. INFO.: DE 1991-4117078 19910525				
WO 1992-EP1080 19920516				

AB From aq.-formulations therapeutic proteins, **aerosols** (for delivery to lung) are produced by ultrasound atomization. The preps. could contain addnl. excipients such as surfactants, emulsifiers, stabilizers and preservatives. An ultrasound atomizer with a frequency of 2-3 MHz is used.

L9 ANSWER 16 OF 17 CAPLUS COPYRIGHT 2003 ACS
 ACCESSION NUMBER: 1988:443473 CAPLUS
 DOCUMENT NUMBER: 109:43473
 TITLE: Device and dispersion for intrapulmonary delivery of polypeptide growth factors and cytokines
 INVENTOR(S): Daugherty, Ann Leslie
 PATENT ASSIGNEE(S): Genentech, Inc., USA
 SOURCE: Eur. Pat. Appl., 10 pp.
 CODEN: EPXXDW
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 257956	A2	19880302	EP 1987-307276	19870818
EP 257956	A3	19890419		
EP 257956	B1	19920520		
EP 257956	B2	20001122		
R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
AT 76311	E	19920615	AT 1987-307276	19870818
ES 2032831	T3	19930301	ES 1987-307276	19870818
JP 63051868	A2	19880304	JP 1987-207361	19870819
JP 2573959	B2	19970122		
CA 1292182	A1	19911119	CA 1987-544836	19870819
US 6099517	A	20000808	US 1993-128058	19930927
US 6402733	B1	20020611	US 2000-552199	20000419
PRIORITY APPLN. INFO.: US 1986-897962 A 19860819				
EP 1987-307276 A 19870818				
US 1989-312325 B1 19890216				
US 1991-762039 B1 19910917				

US 1992-982268 B1 19921125

US 1993-128058 A1 19930927

AB Polypeptides selected from growth factors and cytokines are administered by intrapulmonary inhalation: compressed air entrains a soln. of the polypeptide from a reservoir, and the polypeptide soln. is dispersed by a nebulizer and inhaled directly into the lungs via a mouthpiece. Using the

invention device, an anesthetized baboon was treated for 30 min with somatrem in a mannitol/phosphate buffer, at 22 cm H₂O at a rate of 1.8 mg somatrem/min, allowed to breathe normally for 20 min, and treated again for 30 min. Serum human growth hormone peaked at >280 ng/mL after the second dose, and continued to show elevated levels (>80 ng/mL) after 28

h.

The long term drug delivery is surprising, as it is generally believed that drug deliver of >12 h is not achievable by intrapulmonary inhalation.

L9 ANSWER 17 OF 17

MEDLINE

DUPLICATE 9

ACCESSION NUMBER: 88198993 MEDLINE

DOCUMENT NUMBER: 88198993 PubMed ID: 3283235

TITLE: **Lung-specific delivery of cytokines** induces sustained pulmonary and systemic immunomodulation in rats.

AUTHOR: Debs R J; Fuchs H J; Philip R; Montgomery A B; Brunette E N; Liggitt D; Patton J S; Shellito J E

CORPORATE SOURCE: Cancer Research Institute, University of California, San Francisco 94143.

SOURCE: JOURNAL OF IMMUNOLOGY, (1988 May 15) 140 (10) 3482-8. Journal code: 2985117R. ISSN: 0022-1767.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals

ENTRY MONTH: 198806

ENTRY DATE: Entered STN: 19900308

Last Updated on STN: 19900308

Entered Medline: 19880609

AB The recombinant cytokines IFN-gamma and TNF-alpha stimulate several macrophage-mediated functions important in host defense. However, systemic

administration of cytokines may be limited by significant host toxicity. We investigated whether aerosolized cytokines can stimulate alveolar macrophage and blood monocyte function, and whether they induce an inflammatory response in the lungs of normal rats. We found that aerosolized murine rIFN-gamma or recombinant human TNF-alpha increased IL-1 production by both alveolar macrophages and blood monocytes for at least 5 days after administration. Furthermore, murine rIFN-gamma increased the expression of Ia Ag on alveolar macrophages and human rTNF-alpha increased alveolar macrophage- and blood monocyte-mediated tumor lysis. Sequential aerosolization of IFN-gamma and TNF-alpha significantly increased both IL-1 release and Ia expression compared to either cytokine administered alone. Aerosolized human rTNF-alpha achieved lung levels comparable to those produced by an i.v. TNF-alpha dose reported to cause diffuse organ injury and death in rats. However, plasma TNF-alpha levels were several thousand-fold lower after aerosol administration. Aerosolized cytokines did not induce lung edema or an inflammatory cell infiltrate within the airways or alveoli. Aerosolized human rTNF-alpha alone, or murine rIFN-gamma and human rTNF-alpha, induced

margination of leukocytes in pulmonary blood vessels 1 day after

aerosolization, and a few small foci of pulmonary hemorrhage 5 days later.

We conclude that **aerosol** administration of IFN-gamma or TNF-alpha enhances both pulmonary and systemic monocyte function, and that

the combination of IFN-gamma and TNF-alpha produce additive or synergistic

effects. Aerosolized cytokines induce only a minimal pulmonary inflammatory response. Aerosolized TNF-alpha produces high cytokine levels

in the lung but very low uptake into the circulation.

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SINCE FILE

TOTAL

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SESSION

FULL ESTIMATED COST

68.42

68.63

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

SINCE FILE

TOTAL

ENTRY

SESSION

CA SUBSCRIBER PRICE

-8.46

-8.46

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L4 ANSWER 1 OF 79 CAPLUS COPYRIGHT 2003
ACS

ACCESSION NUMBER: 2002:805245 CAPLUS

DOCUMENT NUMBER: 137:277763

TITLE: Myeloid blood CD11c+ dendritic cells
and

monocyte-derived dendritic cells differ
in their

ability to stimulate T lymphocytes

AUTHOR(S): Osugi, Yuko; Vuckovic, Slavica;
Hart, Derek N. J.

CORPORATE SOURCE: Department of
Developmental Medicine (Pediatrics),
D-5, Osaka University Graduate School
of Medicine,
Japan

SOURCE: Blood (2002), 100(8), 2858-2866
CODEN: BLOOAW; ISSN: 0006-4971

PUBLISHER: American Society of Hematology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Dendritic cells (DCs) initiate and direct immune
responses. Recent

studies have defined different DC populations,

therefore we undertook this

study comparing 2 types of myeloid DCs: blood

CD11c+ DCs and in vitro

monocyte-derived DCs (Mo-DCs), which are both

candidates as cellular

adjuvants for cancer immunotherapy. Blood

CD11c+ DCs were prepd. by cell

sorting from peripheral blood mononuclear cells
cultured overnight in RPMI

1640 medium supplemented with autologous or
pooled AB serum. Mo-DCs were

prepd. in the same medium using granulocyte

macrophage-colony-stimulating

factor (GM-CSF)/interleukin 4 (IL-4) and

differentiated/activated with

lipopolysaccharide or monocyte-conditioned medium

(ActMo-DCs). Morphol.,

differences between the DC preps. were noted

both at a light and electron

microscopic level. Blood CD11c+ DCs expressed

similar levels of HLA-DR,

CD40, CD86, and CD83 as Mo-DCs. CD209 was

present on Mo-DCs but not on

blood CD11c+ DCs. Blood CD11c+ DCs generated

a lower proliferative mixed

leukocyte response (MLR) than Mo-DCs. Blood

CD11c+ DCs loaded with 0.1

.mu.g/mL tetanus toxoid (TT)-generated greater T

lymphocyte proliferative

responses than did Mo-DCs or ActMo-DCs, but

when loaded with higher TT

concns. no difference in T lymphocyte proliferative
response was obsd.

Keyhole limpet hemocyanin (KLH)-loaded blood

CD11c+ DCs generated greater

T lymphocyte proliferative responses than Mo-DCs

or ActMo-DCs. Allogeneic

MLR- or KLH-specific responses induced by blood

CD11c+ DCs generated more

Th1 effectors than the responses induced by Mo-
DCs or ActMo-DCs. These

data establish several differences in the properties
of blood CD11c+ DCs,

Mo-DCs, and ActMo-DCs, which suggest that blood
DCs merit further

consideration as DC preps. for clin. programs are
evolved.

REFERENCE COUNT: 52 THERE ARE 52

CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS

AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 79 MEDLINE

DUPLICATE 1

ACCESSION NUMBER: 2002357112 MEDLINE

DOCUMENT NUMBER: 22095350 PubMed ID:

12100724

TITLE: Regulation of HLA-DR and co-

stimulatory molecule expression

on natural killer T cells by granulocyte-
macrophage

colony-stimulating factor.

AUTHOR: Saikh Kamal U; Kissner Teri; Ulrich
Robert G

CORPORATE SOURCE: Laboratory of Molecular

Immunology, Army Medical Research

Institute of Infectious Diseases, Frederick,
MD 21702-5011,

USA.

SOURCE: IMMUNOLOGY, (2002 Jul) 106 (3)
363-72.

Journal code: 0374672. ISSN: 0019-2805.

PUB. COUNTRY: England: United Kingdom

DOCUMENT TYPE: Journal; Article; (JOURNAL

ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200208

ENTRY DATE: Entered STN: 20020709

Last Updated on STN: 20020829

Entered Medline: 20020828

AB A subset of mononuclear cells present in most

tissues coexpresses

receptors of both natural killer (NK) and T cells.

Although linked to

antiviral immunity, the function of these putative NKT
cells is uncertain.

We present evidence that human CD56+ DR- NKT

cells exhibit hybrid adaptive

and innate immune functions. These cells

spontaneously lysed tumour cell

targets and upon engagement of T-cell antigen

receptors secreted the

cytokines interferon-gamma and granulocyte-

macrophage

colony-stimulating factor (GM-CSF). Conversely,

GM-CSF treatment

transformed the NKT cells into dendritic cells,

inducing rapid expression

of HLA-DR and the co-stimulatory molecules CD80

and

CD86. The ability to stimulate tetanus toxoid-specific
responses

from naive T cells was acquired within 3 days of

activating CD56+ NKT

cells with GM-CSF. These results suggest a

potential role for NKT cells in

the initiation and control of primary immunity during

the acute phase of

infection.

L4 ANSWER 3 OF 79 BIOSIS COPYRIGHT 2003
BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 2002:261703 BIOSIS

DOCUMENT NUMBER: PREV200200261703

TITLE: Flt3 ligand safely increases dendritic
cells after

autologous transplantation which may be
useful to correct

the impaired immune response to neo-
antigens after

autologous transplant.

AUTHOR(S): Miller, Jeffrey S. (1); Weisdorf,
Daniel J. (1);

Panoskaltsis-Mortari, Angela (1);

Curtsinger, Julie R. (1);

Blazar, Bruce R. (1)

CORPORATE SOURCE: (1) Blood and Marrow
Transplant Program, University of

Minnesota, Minneapolis, MN USA

SOURCE: Blood, (November 16, 2001) Vol. 98,
No. 11 Part 1, pp.

860a. <http://www.bloodjournal.org/>. print.

Meeting Info.: 43rd Annual Meeting of the

American Society
of Hematology, Part 1 Orlando, Florida,

USA December 07-11,

2001

ISSN: 0006-4971.

DOCUMENT TYPE: Conference

LANGUAGE: English

AB Relapse is still the most common cause of
treatment failure after

autologous transplant and cancer vaccines may
eradicate minimal residual

disease. However, even the best vaccine strategy
will fail if the immune

system is not able to respond appropriately. To test
immune integrity, we

vaccinated 15 normal volunteers with 1 mg of KLH,
a neo-antigen that

humans would not have been exposed to previously
and 10 received tetanus

toxoid (TT), an antigen that all subjects have seen.

Proliferation assays

were performed in limiting dilutions to allow

frequency calculations. The

frequency of KLH-specific mononuclear cells

increased 20-fold 28 days

after a KLH vaccine and 100% of normal subjects

responded. As expected,

the frequency of TT-specific cells was higher at

baseline and increased

3.6-fold after vaccination. Similar responses were

seen using ELISPOT

readouts for cells producing INF-GAMMA. KLH

elicited potent IgM, IgG1,

IgG2 and IgG3 specific antibody responses in all

normal subjects and

TT-specific IgG1 increased as well. We next

vaccinated 6 patients

(myeloma, CML, breast cancer) 3-19 months after

autologous transplant. In

marked contrast to normal subjects, only 1 of 6

patients exhibited a KLH

proliferative response and 1 of 5 exhibited a TT

response. No patient

mounted a specific humoral response. The poor

response in transplant

patients is of major concern if vaccines are to be
added early when

disease burden is lowest. Since immune integrity is
diminished after

autologous transplant, we explored the role of
outpatient administration

of flt3 ligand given as a subcutaneous injection (20
mug/kg) QOD for a

total of 21 doses in a phase I clinical trial. Patients
were eligible for

this study 56-112 days after autologous transplant if
they had hematologic

recovery and no ongoing therapy related toxicities.

Eight patients have

started Flt3L on this trial and five have completed

therapy. The first

cohort of 5 patients did not receive KLH. There has

been no constitutional

symptoms related to this immunotherapy and no

clinical toxicity or

hospitalizations. Monocytes were increased in all

patients on therapy.

Dendritic cell (DC) numbers determined by 4-color
immunophenotype analysis

from blood at day 14 showed a median 25-fold (4-
52-fold) increase in

CD11c+, HLA-DR+, CD14-DC compared to blood
obtained

prior to initiating therapy. Co-stimulatory molecule
expression (CD80 and

CD86) on in vivo mobilized DC was lower than that
found on monocyte

derived DC generated in vitro. Two of three

evaluable patients had an

increased ability to stimulate an allogeneic mixed
lymphocyte

reaction on day 14 of therapy and the third patient
was unchanged compared

to baseline. There was no significant change in NK
cell numbers or

cytotoxicity assays against K562 targets throughout
the study period

suggesting that NK cells are not stimulated in vivo
by flt3 ligand as

found in the mouse. The next 5 patients on study will

receive KLH to

determine whether flt3 ligand can serve as a vaccine
adjuvant to illicit a

neo-antigen immune response after autologous

transplantation. We conclude

that flt3 ligand can be administered safely early after

autologous

transplant to increase circulating DCs which may be

useful alone or in

combination with other agents to elicit specific anti-
tumor immunity.

L4 ANSWER 4 OF 79 MEDLINE

DUPLICATE 2

ACCESSION NUMBER: 2001161157 MEDLINE

DOCUMENT NUMBER: 21159443 PubMed ID:

11260079

TITLE: Recognition of chronic myelogenous
leukaemia cells by

autologous T lymphocytes primed in vitro
against the

patient's dendritic cells.

AUTHOR: Muller L; Provenzano C; Faul C;

Pawelec G

CORPORATE SOURCE: Tubingen Ageing and
Tumour Immunology Group (TATI), Section

for Transplantation Immunology, University
of Tübingen,
Otfried-Müller Str. 10, D-72076 Tübingen,
Germany..

ludmilla.mueller@med.uni-tuebingen.de
SOURCE: BRITISH JOURNAL OF
HAEMATOLOGY, (2001 Mar) 112 (3) 740-8.
Journal code: 0372544. ISSN: 0007-1048.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL
ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200104
ENTRY DATE: Entered STN: 20010417
Last Updated on STN: 20010417
Entered Medline: 20010412

AB Defects in immune responses are common in
patients with chronic
myelogenous leukaemia (CML). However, using
dendritic cells (DCs) to
promote T-cell immunity in vitro may nonetheless
elicit potent specific
anti-tumour responses for use in immunotherapy.
Here, we show that DCs
generated from CML patients had a typical dendritic
phenotype and were
able to stimulate autologous T cells. Three primed T-
cell lines
were studied in more detail in one patient. They
were stimulated by
autologous CML cells, but not by normal non-
leukaemic cells from the
patient's HLA-identical sibling. This was blocked by
HLA-
DR-specific, but not HLA-DQ- or HLA-DP-specific
antibodies.
CML-stimulated cytokine secretion, including
interferon-
gamma and granulocyte macrophage-colony
stimulating factor,
suggested a Th1-type phenotype for these
sensitized anti-leukaemic T
cells. This study therefore shows that cells with a
functional dendritic
phenotype can be generated from the blood of CML
patients and are potent
inducers of T-cell responses to tumour cells. This
approach allows
sensitization of patients' T cells by their own
particular tumour without
the need to identify the exact leukaemia antigens
involved, and may find
application in immunotherapy of CML.

L4 ANSWER 5 OF 79 BIOSIS COPYRIGHT 2003
BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 2002:186773 BIOSIS

DOCUMENT NUMBER: PREV200200186773

TITLE: Feasibility of immunotherapy using
donor CD8+ T cells

stimulated with leukemic cell- or donor
CD14+ cell derived
dendritic cells (DC) against leukemia
relapsing after

hematopoietic stem cell transplantation
(HSCT).

AUTHOR(S): Lee, Je-Jung (1); Chung, Ik-Joo (1);
Kook, Hoon (1); Hwang,

Tai-Ju (1); Nam, Chan-Eun (1); Nam,
Jong-Hee; Lee,
Hyun-Cheol; Takaue, Yoichi; Kim,
Hyeoung-Joon (1)
CORPORATE SOURCE: (1) Blood and Marrow
Transplant Program, Chonnam National
University Medical School, Gwangju South
Korea
SOURCE: Blood, (November 16, 2001) Vol. 98,
No. 11 Part 1, pp.
388a. <http://www.bloodjournal.org/>. print.
Meeting Info.: 43rd Annual Meeting of the
American Society
of Hematology, Part 1 Orlando, Florida,
USA December 07-11,
2001
ISSN: 0006-4971.

DOCUMENT TYPE: Conference

LANGUAGE: English

AB In relapsing leukemia after allogeneic HSCT,
donor lymphocyte infusions

(DLI) have been used as a salvage therapy based
on the

graft-versus-leukemia effect mediated by T-cell
effectors. Though

effective in the chronic phase of CML, the potential
of DLI has been

limited in patients with AML, ALL, or MDS. DLI is
further complicated by

the induction of acute graft-versus-host disease
(GVHD) or bone marrow

aplasia. To overcome these problems, a possible
alternative approach

includes the application of selected immune effector
cells. In addition to

difficulty to generate them, however, leukemic cell-
derived DC

(leukemic-DC) have been hampered by the
inadequate potency of T-cell

stimulation due to the lower expression of molecules
related to adhesion,

MHC, and the costimulatory pathway compared to
normal DC. For leukemia

relapsing after allogeneic HSCT, we investigated the
possibility of

immunotherapy using target-specific donor CD8+ T
cells, which were

generated by leukemic-DC or donor CD14+ cell-
derived DC (donor-DC) pulsed

with leukemic cell lysates. To generate leukemic-
DC, mononuclear cells

isolated from leukemic patients who relapsed after
transplantation were

cultured in medium with GM-CSF (100 ng/mL), IL-4
(100 ng/mL), and

TNF-alpha (50 ng/mL) for 8-10 days.

Simultaneously, CD14+ cells were

isolated from HLA-matched donors using Mini-
MACS, and cultured with GM-CSF

(50 ng/mL) and IL-4 (50 ng/mL). Maturation of
donor-DC was induced by the

addition of TNF-alpha on day 6 and the DC were
harvested on day 9. For

evaluation of leukemic-DC and donor-DC,
morphologic studies using

May-Grunwald-Giemsa staining, phenotypic studies
using several mouse

monoclonal antibodies, allogeneic mixed lymphocyte
reaction for normal

donor CD3+ T cells using 3(H)-methylthymidine, and FISH analysis were performed. For cytotoxic assay, CD8+ T cells isolated from a transplant donor using Mini-MACS were stimulated on days 0 and 10 by leukemic-DC or donor-DC which were pulsed with leukemic cell lysates, and further cocultured with leukemic cells to perform LDH assay or IFN-gamma ELISA on day 20. We observed that cells from both groups showed similar typical features of mature DC. The leukemic-DC were derived from original leukemic cells, as shown by -7 or bcr/abl rearrangement using FISH analysis.

Although leukemic-DC highly expressed HLA-DR and CD54, the expression of CD80, CD83, CD86, CD1a, and CD40 on leukemic-DC was significantly lower compared to donor-DC. Donor-DC had a higher capacity to stimulate allogeneic CD3+ T cells compared to leukemic-DC.

Donor CD8+ T cells stimulated by leukemic-DC or donor-DC have more potent cytotoxic activity than unprimed CD8+ T cells, while a slightly higher cytotoxicity was observed in donor-DC compared to leukemic-DC. These

results suggest that donor CD8+ T cells stimulated with leukemic-DC or donor-DC be feasible as an alternative immunotherapy to DLI for the application to leukemic patients who relapse after allogeneic HSCT, although further studies are needed to investigate the clinical efficacy and the potential risk of GVHD associated with this strategy.

L4 ANSWER 6 OF 79 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE

3

ACCESSION NUMBER: 2000:486589 BIOSIS
DOCUMENT NUMBER: PREV200000486589
TITLE: Role and expression of CD40 on human retinal pigment epithelial cells.

AUTHOR(S): Willermain, Francois (1); Caspers-Velu, Laure; Baudson, Nathalie; Dubois, Christine; Hamdane, Malika; Willems, Fabienne; Velu, Thierry; Bruyns, Catherine
CORPORATE SOURCE: (1) ULB, Cmpus Erasme, I.R.I.B.H.N., Route de Lennik 808, Building C, 6th Floor, Room C6 117, Bruxelles Belgium

SOURCE: IOVS, (OCTOBER, 2000) Vol. 41, No. 11, pp. 3485-3491.
print.

DOCUMENT TYPE: Article

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Purpose: To examine the CD40 costimulatory molecule expression on normal resting or activated adult human retinal pigment epithelium (hRPE) cells and to evaluate its role as an activation molecule considering the

potential antigen presentation functions of hRPE cells. Methods:

Expression of HLA-DR and costimulatory (CD40, B7.1,

B7.2, CD54, and CD58) molecules on hRPE cells was analyzed by flow

cytometry. CD40 triggering was performed using soluble CD40L or cocultures

with CD40L transfected fibroblasts. Interleukin (1L)-6, -8, -10, and -12

secretions were measured by enzyme-linked immunosorbent assay. Antigen

presentation function of hRPE cells was assessed by coculturing hRPE cells

with allogeneic T cells. T-cell proliferation was measured by

(3H)-thymidine incorporation, and T-cell apoptosis by measurement of

caspase-3 activity. Results: Interferon (IFN) gamma-activated hRPE cells

expressed CD40 but not B7.1 or B7.2. Although interferon

gamma enhanced IL-6 and IL-8 production, CD40 triggering of IFN

gamma-activated hRPE cells did not induce IL-12 secretion. hRPE cells did

not stimulate allogeneic resting T cells and downregulated

phytohemagglutinin-activated allogeneic T cells via a cell-to-cell

contact-dependent mechanism. Some induction of apoptosis was detected.

Conclusions: CD40 is expressed on IFN gamma-activated hRPE cells. Its

ligation leads to an increased production of IL-6 and IL-8 but fails to

induce B7.1 or B7.2 expression, or to induce IL-12 secretion. Accordingly,

hRPE cells do not activate allogeneic T cells but inhibit T-cell

proliferation, partly through induction of apoptosis. These results

suggest that hRPE cells could be implicated more in a deviant antigen

presentation. If the exact molecular mechanisms are unclear, it is likely

that CD40-CD40L interaction could play a role in this process.

L4 ANSWER 7 OF 79 MEDLINE

DUPLICATE 4

ACCESSION NUMBER: 2002047725 MEDLINE

DOCUMENT NUMBER: 21632502 PubMed ID: 11776063

TITLE: Effect of immunoglobulin G from patients with Graves'

ophthalmopathy and interferon gamma in intercellular adhesion molecule-1 and

human leucocyte

antigen-DR expression in human retroocular fibroblasts.

AUTHOR: Li Y; Chen L; Teng W; Shan Z; Li Z

CORPORATE SOURCE: Department of Endocrinology, First Clinical College, China Medical University, Shenyang 110001, China.

SOURCE: CHINESE MEDICAL JOURNAL,

(2000 Aug) 113 (8) 752-5.

Journal code: 7513795. ISSN: 0366-6999.

PUB. COUNTRY: China

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200202

ENTRY DATE: Entered STN: 20020125

Last Updated on STN: 20020202

Entered Medline: 20020201

AB OBJECTIVE: To detect the expression of intercellular adhesion molecule-1 (ICAM-1) and human leucocyte antigen-DR (HLA-DR) on

retroocular fibroblasts (RFs) by immunoglobulin G (IgG) from patients with Graves' ophthalmopathy (GO) and interferon gamma

(IFN-gamma) and to study the possible mechanism of humoral immunity and cellular immunity in the pathogenesis of GO.

METHODS: Purified IgG was obtained from 23 patients (GO 10, Graves' disease 9, toxic multinodular goiter 4) and 8 normal persons. Cytokine IFN-gamma and thyroid stimulating hormone (TSH) were incubated with normal human RF cultured in vitro.

Antigen expression on RFs induced by stimulators was examined using immunofluorescence staining and a flow cytometer.

RESULTS: RFs spontaneously expressed ICAM-1, but did not express HLA-

DR. All IgGs from patients with GO and other thyroid diseases as well as from normal persons could not stimulate the expression

of ICAM-1 on RFs. IFN-gamma and TSH significantly enhanced the expression of ICAM-1 in dose-dependent manner ($P < 0.05$).

Only IFN-gamma could stimulate RFs to express HLA-DR ($P < 0.05$).

CONCLUSIONS: IgG from patients with GO did not stimulate the expression of ICAM-1 and HLA-DR on the surface of cultured normal human RFs. IFN-gamma was the important factor for initiating and promoting autoimmune reactions in GO. We need to pay more attention to TSH, as it may possibly play a promoting role in the pathogenesis in GO.

L4 ANSWER 8 OF 79 MEDLINE

DUPLICATE 5

ACCESSION NUMBER: 2000117955 MEDLINE

DOCUMENT NUMBER: 20117955 PubMed ID: 10652024

TITLE: Accessory role of human peritoneal mesothelial cells in

antigen presentation and T-cell growth.

AUTHOR: Hausmann M J; Rogachev B; Weiler M; Chaimovitz C;

Douvdevani A

CORPORATE SOURCE: Department of Nephrology, Soroka Medical Center, Ben-Gurion

University of the Negev, Faculty of Health

Sciences,

Beer-Sheva, Israel.

SOURCE: KIDNEY INTERNATIONAL, (2000 Feb) 57 (2) 476-86.

Journal code: 0323470. ISSN: 0085-2538.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200003

ENTRY DATE: Entered STN: 20000320

Last Updated on STN: 20000320

Entered Medline: 20000309

AB BACKGROUND: To assess the role of human peritoneal mesothelial cells (HPMCs) in the generation of an immune response during peritonitis, we

tested their ability to activate T-cells by antigen presentation (AP) and by the secretion of interleukin-15 (IL-15). IL-15 is a potent leukocyte

activator that stimulates the proliferation of CD4+, CD8+, and B

and natural killer (NK) cells. METHODS: HPMC and mononuclear cells were derived from six volunteer patients who underwent elective abdominal

surgery. Flow cytometry was used to analyze human lymphocyte antigen-DR (HLA-DR), intercellular adhesion molecule-1 (ICAM-1), and

B7 molecules on HPMC. Affinity-purified CD4 cells were used for AP

assays. We used a specific enzyme-linked immunosorbent assay to detect interferon-gamma (IFN-gamma), IL-2, and IL-15

protein and reverse transcription-polymerase chain reaction for mRNA analysis.

RESULTS: HPMC expressed HLA-DR molecules following

IFN-gamma treatment. ICAM-1 molecules were expressed at high levels, and

B7-1 and B7-2 molecules could not be detected. The accessory function of

HPMC was assayed by T-cell stimulation using anti-CD3 antibodies (OKT3).

HPMC were essential for a significant OKT3-induced T-cell proliferation.

Anti-ICAM-1 antibodies blocked OKT3-induced proliferation. HPMC served as effective antigen-presenting cells when Tetanus toxoid (TT) or

Staphylococcus aureus-alpha-toxin were used as antigens. IFN-gamma, IL-2,

and IL-15 accumulated during AP reactions. We found that IL-15 is produced

by HPMC, and IFN-gamma up-regulated its mRNA levels and protein secretion

in a dose-dependent manner. We also detected IL-15 in the peritoneal

effluent of patients undergoing continuous peritoneal dialysis treatment.

In patients suffering from peritonitis, IL-15 levels were elevated (35.0

+/- 6.0 pg/mL, N = 10) as compared with noninfected patients (16.2 +/- 4.0

pg/mL, N = 7). CONCLUSIONS: HPMC participate in the peritoneal immune

response against invading pathogens by AP. For this process, ICAM-1 is the

major accessory molecule. In addition, HPMC may contribute to T-cell

activation by secretion of IL-15.

L4 ANSWER 9 OF 79 MEDLINE

DUPLICATE 6

ACCESSION NUMBER: 2000241576 MEDLINE

DOCUMENT NUMBER: 20241576 PubMed ID:
10780664

TITLE: CD4+ T cell-mediated cytotoxicity
toward thyrocytes: the
importance of Fas/Fas ligand interaction
inducing apoptosis
of thyrocytes and the inhibitory effect of
thyroid-stimulating hormone.

AUTHOR: Kawakami A; Matsuoaka N; Tsuboi M;
Koji T; Urayama S; Sera
N; Hida A; Usa T; Kimura H; Yokoyama N;
Nakashima T;

Ishikawa N; Ito K; Kawabe Y; Eguchi K
CORPORATE SOURCE: The First Department of
Internal Medicine, Nagasaki
University School of Medicine, Tokyo,
Japan.

SOURCE: LABORATORY INVESTIGATION,
(2000 Apr) 80 (4) 471-84.

Journal code: 0376617. ISSN: 0023-6837.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL
ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200005

ENTRY DATE: Entered STN: 20000518

Last Updated on STN: 20000518

Entered Medline: 20000509

AB The accumulation of activated CD4+ T cells and
antigen (Ag)-dependent
cellular interactions between thyrocytes and CD4+ T
cells have been

determined in thyroid gland from patients with
Graves' disease. The
Fas/Fas ligand (FasL) interaction between antigen-
presenting cells and T
cells regulates the apoptosis of the former cells
triggered by the latter

cells. The inhibition of Fas-mediated apoptosis in
thyrocytes could be a
underlying mechanism of hyperplasia of thyrocytes
in patients with Graves'
disease. We investigated the potential role of

Fas/FasL interaction
between thyrocytes and CD4+ T cells in the
induction of Fas-mediated
apoptosis of the former cells induced by the latter
cells. The presence of

only a few specific T cells responsive to a putative
autoantigen has
hampered the investigation of specific T cell
activation toward

antigen-presenting cells (APCs). Therefore, we used
a superantigen,
staphylococcal enterotoxin B (SEB), to examine
specific T cell activation

toward thyrocytes in vitro since it stimulates a large
proportion of T cells with particular Vbeta elements.
Spontaneous

apoptosis of thyrocytes in culture was not found
even in the presence of
various kinds of cytokines. In contrast, a clear
induction of Fas-mediated

apoptosis by anti-Fas IgM was determined in
interferon-

gamma (IFN-gamma)-stimulated thyrocytes. In
addition, a

significant cytotoxicity of purified CD4+ T cells
toward

IFN-gamma-stimulated thyrocytes in the presence of
SEB was induced, and
the addition of anti-HLA-DR and -DQ monoclonal
antibodies (mAbs) or blockade of the Fas/FasL
interaction reduced this
cytotoxicity. FasL expression of CD4+ T cells
cocultured with

IFN-gamma-stimulated thyrocytes in the presence of
SEB was clearly

induced. Furthermore, the addition of mAbs against
CD54 and CD58 inhibited

both cytotoxicity and FasL expression of CD4+ T
cells. The cytotoxicity of

CD4+ T cells toward IFN-gamma-stimulated, SEB-
pulsed thyrocytes was

markedly inhibited when we used thyrocytes
cultured with IFN-gamma in the
presence of thyroid-stimulating hormone (TSH) as
target cells. Our results

suggest that 1) CD4+ T cells were activated by
thyrocytes expressing MHC
class II molecules in an SEB-dependent manner and
then expressed FasL. 2)

These activated FasL+ CD4+ T cells killed
thyrocytes by interacting with

Fas on thyrocytes and FasL on activated CD4+ T
cells. The presence of

costimulating molecules such as CD54 and CD58 on
thyrocytes was also

necessary to generate activated FasL+ CD4+ T
cells. 3) Since the actions

of thyroid stimulating antibody (TSAb) toward
thyrocytes are similar to
those of TSH, one goitrogenic activity of TSAb may,
in part, be due to the

inhibitory effect on Fas-mediated apoptosis of
thyrocytes triggered by
activated CD4+ T cells.

L4 ANSWER 10 OF 79 BIOSIS COPYRIGHT 2003
BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 2001:314818 BIOSIS

DOCUMENT NUMBER: PREV200100314818

TITLE: In vitro priming of normal donor PBMC
with myeloma

protein pulsed dendritic cells.

AUTHOR(S): Kim, S. B. (1); Baskar, S.; Kwak, L.
W.

CORPORATE SOURCE: (1) Department of Medicine,
Asan Medical Center, University
of Ulsan, Seoul South Korea

SOURCE: Blood, (November 16, 2000) Vol. 96,
No. 11 Part 2, pp.

289b, print.

Meeting Info.: 42nd Annual Meeting of the
American Society

of Hematology San Francisco, California,
USA December

01-05, 2000 American Society of
Hematology

. ISSN: 0006-4971.

DOCUMENT TYPE: Conference

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Dendritic cells (DC) are very efficient antigen-presenting cells (APC) and have been used to directly present exogenous antigen to CD8+ T cells. In vitro priming of T cells with DC pulsed with weak antigens such as tumor idiotype (Id), is an attractive strategy to generate tumor-specific cytotoxic T lymphocytes (CTL). A previous report from this laboratory demonstrated generation of tumor-specific CTL using autologous DC pulsed with patient Id (Blood, Oct. 15, 2000). In the present study, we extend our investigation to generate antigen-specific T cells from normal donor PBMC by in vitro priming using autologous DC as APC. After 2hr of incubation of PBMC, adherent cells were cultured for generation of DC with IL-4 and GM-CSF, and DC were harvested on different days. Phenotypic analysis showed that DC obtained at day 8, day 10, and day 12 expressed high levels of HLA-DR. The expression of CD80, CD83 and CD86, however, were higher in DC obtained at day 8 compared to those at day 10 and day 12. We compared the ability of DC to stimulate T cell cytokine responses to keyhole limpet, hemocyanin (KLH), tetanus toxoid (TT), and Id. In vitro primed T cells (2-4 cycles of stimulation with Ag and DC) showed significant cytokine responses (IFN γ , TNF α , GM-CSF, IL-13) to TT. Similarly, in vitro priming of T cells with Id-pulsed DC resulted in marked increase in TNF α production (188 pg/ml), compared with unpulsed DC (<15 pg/ml). These data suggest that multiple in vitro immunization using DC as APC could be beneficial in generating tumor specific T cells from normal donor PBMC, which may be used for adoptive immunotherapy (e.g. donor lymphocyte infusion) of B cell malignancies. Thus, in vitro immunization can be a better alternative approach than immunization of stem cell transplant donor with tumor antigen.

L4 ANSWER 11 OF 79 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
 ACCESSION NUMBER: 2001:300013 BIOSIS
 DOCUMENT NUMBER: PREV200100300013
 TITLE: Differential cytokine profiles of leukaemic blasts and leukaemic dendritic cells: Implications for immunotherapy.
 AUTHOR(S): Panoskaltsis, Nicki (1); Knight, Stella C. (1); Reid, Cecil D. L.
 CORPORATE SOURCE: (1) Antigen Presentation Research Group, Imperial College at Northwick Park Institute for Medical Research, Harrow UK

SOURCE: Blood, (November 16, 2000) Vol. 96, No. 11 Part 2, pp. 215b. print.
 Meeting Info.: 42nd Annual Meeting of the American Society of Hematology San Francisco, California, USA December 01-05, 2000 American Society of Hematology

ISSN: 0006-4971.
 DOCUMENT TYPE: Conference
 LANGUAGE: English
 SUMMARY LANGUAGE: English
 AB Dendritic cells (DCs) generated from leukaemic blasts are being evaluated for use in the immunotherapy of leukaemia. DCs can be cultured from most subtypes of AML blasts in approximately 50-75% of samples. These leukaemic DCs (LDCs) are derived from the leukaemic clone and are similar to mature DCs in their expression of surface markers and in their capacity to stimulate lymphocytes. However, stimulation of cytotoxicity against the original AML blasts using T cells expanded with LDCs has had limited success. These cytotoxicity results may be partly explained by the different methods used to generate the LDCs, in particular, the cytokines used in the culture. AML bone marrow mononuclear cells were cultured in serum-free medium for 4-5 and 13-14 days in the presence of granulocyte-macrophage colony stimulating factor and stem cell factor and supplemented with one of the following cytokines: tumour necrosis factor(TNF)-alpha, interleukin(IL)-4, IL-12, or flt-3 ligand (FL). Cells were evaluated by flow cytometry for DC surface markers, CD80, CD86, CD1a, CD40, CD11c, and HLA-DR, as well as for intracellular cytokines IL-4, IL-10, IL-12, and interferon(IFN)-gamma in the presence and absence of calcium ionophore, and the vesicular-transport inhibitor, monensin. Prior to culture, the AML blasts were skewed towards a type 2 cytokine profile, and in particular, showed IL-10 production out of proportion to the other cytokines. After culture, the cytokine profile of the LDC was influenced differentially, depending on the cytokine cocktails used. Exposure to TNF-alpha during the entire culture period, did not polarise the cells towards type 1 or type 2 cytokine production, but IL-4 caused the cultured cells to produce more IL-4. IL-12 exposure induced type 1 cytokines, namely IL-12 and IFN-gamma. In contrast, FL upregulated both type 1 and type 2 cytokines. Interestingly, IL-10 production by the leukaemic blasts was abrogated in all culture conditions. In one sample,

although IL-4 induced more IL-4 in the cells at day 5, the day 14

IFN-gamma expression increased to a fluorescence intensity beyond that of

the other samples. These results show that LDCs can be differentially skewed towards a type 1 or type 2 profile, and imply that the cytokine

conditioning of these cells is critical for an effective anti-leukaemic response.

L4 ANSWER 12 OF 79 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 2001:299456 BIOSIS

DOCUMENT NUMBER: PREV200100299456

TITLE: In vitro priming of normal donor PBMC with myeloma protein pulsed dendritic cells.

AUTHOR(S): Kim, S. B. (1); Baskar, S.; Kwak, L. W.

CORPORATE SOURCE: (1) Department of Medicine, Asan Medical Center, University of Ulsan, Seoul South Korea

SOURCE: Blood, (November 16, 2000) Vol. 96, No. 11 Part 1, pp.

166a. print.

Meeting Info.: 42nd Annual Meeting of the American Society of Hematology San Francisco, California, USA December

01-05, 2000 American Society of

Hematology

. ISSN: 0006-4971.

DOCUMENT TYPE: Conference

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Dendritic cells (DC) are very efficient antigen-presenting cells (APC) and

have been used to directly present exogenous antigen to CD8+ T cells. In

vitro priming of T cells with DC pulsed with weak antigens such as tumor

idiotype (Id), is an attractive strategy to generate tumor-specific

cytotoxic T lymphocytes (CTL). A previous report from this laboratory

demonstrated generation of tumor-specific CTL using autologous DC pulsed

with patient Id (Blood, Oct. 15, 2000). In the present study, we extend

our investigation to generate antigen-specific T cells from normal donor

peripheral blood mononuclear cells (PBMC) by in vitro priming using

autologous DC as APC. After 2hr of incubation of PBMC, adherent cells were

cultured for generation of DC with IL-4 and GM-CSF, and DC were harvested

on different days. Phenotypic analysis showed that DC obtained at day 8,

day 10, and day 12 expressed high levels of HLA-DR.

The expression of CD80, CD83 and CD86, however, were higher in DC obtained

at day 8 compared to those at day 10 and day 12.

We compared the ability

of DC to stimulate T cell cytokine responses to keyhole limpet

hemocyanin (KLH), tetanus toxoid (TT), and Id. In vitro primed T cells

(2-4 cycles of stimulation with Ag and DC) showed significant cytokine

responses (IFNgamma, TNFalpha, GM-CSF, IL-13) to TT. Similarly, in vitro

priming of T cells with Id-pulsed DC resulted in marked increase in

TNFalpha production (188 pg/ml), compared with unpulsed DC (< 15 pg/ml).

These data suggest that multiple in vitro immunization using DC as APC

could be beneficial in generating tumor specific T cells from normal donor

PBMC, which may be used for adoptive immunotherapy (e.g. donor lymphocyte

infusion) of B cell malignancies. Thus, in vitro immunization can be a

better alternative approach than immunization of stem cell transplantation

donor with tumor antigen.

L4 ANSWER 13 OF 79 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2000:503737 CAPLUS

DOCUMENT NUMBER: 133:88037

TITLE: Effects of IgG from patients with Graves'

ophthalmopathy and interferon-gamma (IFN-gamma.) on intercellular

adhesion molecule-1,

HLA-DR expression of human

retroocular fibroblasts

AUTHOR(S): Li, Yushu; Chen, Lei; Teng, Weiping; Shan, Zhongyan;

Li, Zhongmin

CORPORATE SOURCE: Department of Endocrinology, the First Clinical

College, China Medical University,

Shenyang, 110001,

Peop. Rep. China

SOURCE: Zhonghua Neifenmi Daixie Zazhi (2000), 16(3), 146-149

CODEN: ZNDZEK; ISSN: 1000-6699

PUBLISHER: Shanghaishi Neifenmi Yanjiuso

DOCUMENT TYPE: Journal

LANGUAGE: Chinese

AB The effects of IgG from the patients with Graves' ophthalmopathy (GO) and

IFN-gamma. on the expressions of intercellular adhesion mol.-1 (ICAM-1),

HLA-DR on retroocular fibroblasts were assayed to study the possible

mechanism of humoral immunity and cellular immunity in the pathogenesis of

GO. The purified IgGs from 21 patients (10 cases of GO, 7 cases of

Graves' disease, 4 cases of toxic nodular goiter) and 8 normal subjects,

cytokine IFN-gamma. and TSH (TSH) were incubated with normal human RFs in

vitro. Antigen expressions of RFs induced by stimulators were examd. by

flow cytometer after immunofluorescence staining. Normal RFs

spontaneously and partly expressed ICAM-1, but did not express HLA-DR.

All of the IgGs from the patients with GO and other thyroid disease and

normal subjects could not stimulate the expressions of ICAM-1 and HLA-DR of RFs. IFN- γ and TSH significantly enhanced the expression of ICAM-1 of RFs in dose-dependent manners ($P < 0.05$). Only IFN- γ could stimulate RFs to express HLA-DR ($P < 0.05$). IgG from the patients with GO could not stimulate the expressions of ICAM-1 and HLA-DR on the surface of cultured normal human RFs; IFN- γ might be the important factor for initiating and promoting autoimmune reactions in GO; In addn., more attention should be paid to TSH which possibly plays a promoting role in the pathogenesis of GO.

L4 ANSWER 14 OF 79 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 2000:114570 BIOSIS

DOCUMENT NUMBER: PREV200000114570

TITLE: Characterization of tissue outgrowth developed in vitro in

patients with rheumatoid arthritis:

Involvement of T cells

in the development of tissue outgrowth.

AUTHOR(S): Wakisaka, Sueshige; Suzuki, Noboru; Nagafuchi, Hiroko;

Takeba, Yuko; Kaneko, Atsushi; Asai,

Tomiaki; Sakane,

Tsuyoshi (1)

CORPORATE SOURCE: (1) Departments of Immunology and Medicine, St. Marianna

University School of Medicine, 2-16-1,

Sugao, Miyamae-ku,

Kawasaki, Kanagawa, 216-8511 Japan

SOURCE: International Archives of Allergy and Immunology, (Jan.,

2000) Vol. 121, No. 1, pp. 68-79.

ISSN: 1018-2438.

DOCUMENT TYPE: Article

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Background: The aim of this study was to analyze cellular and cytokine

interactions governing the development of synovial tissue outgrowth in

patients with rheumatoid arthritis (RA). Methods: A single-cell suspension

of dissociated synovial tissues of RA patients was cultured for a long

period to develop tissue outgrowth. The resulting tissue outgrowth was

characterized by immunohistochemical staining and ELISA. Results: The

tissue outgrowth developed in vitro included various cell types, such as

macrophage-like synovial cells, fibroblast-like synovial cells and

lymphocytes. Even after prolonged cultivation, synovial cells devoid of

infiltrating T lymphocytes did not form tissue outgrowth. The outgrowth

contained CD3+ cells, LeuM3 (CD14)+ cells and HLA-DR+

cells. The T cells expressed lymphocyte function-associated antigen

(LFA)-1 and CD2, and the synovial cells expressed intracellular adhesion

molecule (ICAM)-1 and LFA-3, suggesting possible interactions via

LFA-1/ICAM-1 and CD2/LFA-3. Production of T-cell derived IFN- γ and

IL-17 and synovial-cell-derived fibroblast growth factor (FGF)-1 and IL-15

was confirmed in the tissue outgrowth as well as in RA synovial tissue.

These cell types stimulate each other by secreting cytokines,

leading to the secretion of proinflammatory cytokines and matrix

metalloproteinase (MMP)-1 by the tissue outgrowth and proliferation of

both lymphocytes and synovial cells. Conclusion:

This study emphasizes the

importance of cellular interactions between T cells and synovial cells,

via adhesion molecules and the secretion of cytokines with stimulatory

activity towards other cell types, for the hyperactivity of RA synovial cells.

L4 ANSWER 15 OF 79 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 2001:291475 BIOSIS

DOCUMENT NUMBER: PREV200100291475

TITLE: Anti-tumor CTL induction by exosomes secreted by human

dendritic cells.

AUTHOR(S): Takahashi, Masuhiro (1); Narita, Miwako; Liu, Aichun;

Kanda, Tatsuo; Fuse, Ichiro; Furukawa,

Tatsuo; Toba, Ken;

Aizawa, Yoshifuwa

CORPORATE SOURCE: (1) School of Health Sciences, Faculty of Medicine, Niigata

University, Niigata Japan

SOURCE: Blood, (November 16, 2000) Vol. 96, No. 11 Part 1, pp. 33a.

print.

Meeting Info.: 42nd Annual Meeting of the

American Society

of Hematology San Francisco, California,

USA December

01-05, 2000 American Society of

Hematology

. ISSN: 0006-4971.

DOCUMENT TYPE: Conference

LANGUAGE: English

SUMMARY LANGUAGE: English

AB In order to establish an efficient cell-free

immunotherapy for tumors, we

examined antigen presenting and CTL inducing functions of exosomes

secreted by human dendritic cells. Dendritic cells were generated by

culture of human peripheral adherent cells in serum-free, 1% autoserum or

10% FBS medium containing GM-CSF (100 ng/ml) and IL-4 (10 ng/ml) with or

without IFN- γ (500 U/ml) or IL-10 (10 ng/ml). Dendritic cells were

generated also by the culture of peripheral blood mononuclear cells with

calcium ionophore, A23187 (375-750 ng/ml).

Exosomes were prepared from

supernatants of dendritic cell culture by centrifugation method.

Supernatants were centrifuged at 10,000 g for eliminating cell debris and then at 100,000 g for spinning down exosomes as pellets. For preparing exosomes containing antigenic tumor peptides, dendritic cells, which were generated from persons with HLA-A24 by culture in 1% autoserum containing medium with GM-CSF and IL-4, were pulsed with 9mer SART-1 peptides (donated by Dr. K Itoh, Kurume, Japan) on day 6 of culture and exosomes were prepared on day 7. Antigen presenting function of exosomes were evaluated by 3H-thymidine uptake of allogeneic lymphocytes cultured with exosomes for 5 day. CTL inducing function of exosomes were evaluated by 51Cr-release assay using repeatedly exosome-primed, then IL-2 stimulated autologous lymphocytes as effectors and KE4 (HLA-A24 positive and SART-1 expressing cell line) or the same dendritic cells pulsed with SART-1 peptides as targets. Dendritic cells cultured with GM-CSF & IL-4 with or without IFN-gamma or IL-10 were demonstrated to secrete exosomes which stimulate allogeneic lymphocyte proliferation. By culture of peripheral blood mononuclear cells with A23187 for 4 days, dendritic cells expressing CD83, CD80, CD86 and HLA-DR were generated and were demonstrated to secrete exosomes which stimulate allogeneic lymphocyte proliferation. Dendritic cells pulsed with SART-1 peptides were shown to secrete exosomes which induce CTL against KE4 or autologous dendritic cells pulsed with the peptides. These findings revealed that dendritic cell derived exosomes with antigen presenting and CTL inducing function are applicable to anti-tumor immunotherapy.

L4 ANSWER 16 OF 79 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
 ACCESSION NUMBER: 2000:317063 BIOSIS
 DOCUMENT NUMBER: PREV200000317063
 TITLE: Major peptide autoepitopes for nucleosome-specific T cells of human lupus.
 AUTHOR(S): Lu, Liangjun; Kaliyaperumal, Arunan; Boumpas, Dimitrios T.; Datta, Syamal K. (1)
 CORPORATE SOURCE: (1) Arthritis Division, Northwestern University Medical School, 303 East Chicago Avenue, Ward 3-315, Chicago, IL, 60611-3008 USA
 SOURCE: Journal of Clinical Investigation, (August, 1999) Vol. 104, No. 3, pp. 345-355. print.
 ISSN: 0021-9738.
 DOCUMENT TYPE: Article
 LANGUAGE: English

SUMMARY LANGUAGE: English
 AB We tested 154 peptides spanning the entire length of core histones of nucleosomes for the ability to stimulate an anti-DNA autoantibody-inducing T helper (Th) clone, as well as CD4+ T-cell lines and T cells, in fresh PBMCs from 23 patients with lupus erythematosus. In contrast to normal T cells, lupus T cells responded strongly to certain histone peptides, irrespective of the patient's disease status. Nucleosomal peptides in histone regions H2B10-33, H416-39 (and overlapping H414-28), H471-94, and H391-105 (and overlapping H3100-114) were recurrently recognized by CD4 T cells from the patients with lupus. Remarkably, these same peptides overlap with major epitopes for the Th cells that induce anti-DNA autoantibodies and nephritis in lupus-prone mice. We localized 2 other recurrent epitopes for human lupus T cells in H2A34-48 and H449-63. All the T-cell autoepitopes have multiple HLA-DR binding motifs, and the epitopes are located in histone regions recognized by lupus autoantibodies, suggesting a basis for their immunodominance. Native nucleosomes and their peptides H416-39, H471-94, and H391-105 induced a stronger IFN-gamma response, whereas others, particularly, H2A34-48, favored an IL-10-and/or IL-4-positive T-cell response. The major autoepitopes may reveal the mechanism of autoimmune T-cell expansion and lead to antigen-specific therapy of human lupus.

L4 ANSWER 17 OF 79 MEDLINE
 DUPLICATE 7
 ACCESSION NUMBER: 1999373628 MEDLINE
 DOCUMENT NUMBER: 99373628 PubMed ID: 10444257
 TITLE: T cell proliferation, MHC class II restriction and cytokine products of gliadin-stimulated peripheral blood mononuclear cells (PBMC).
 AUTHOR: O'Keeffe J; Mills K; Jackson J; Feighery C
 CORPORATE SOURCE: Department of Immunology, St James's Hospital, Dublin, Ireland.. okeeffej@tcd.ie
 SOURCE: CLINICAL AND EXPERIMENTAL IMMUNOLOGY, (1999 Aug) 117 (2) 269-76.
 Journal code: 0057202. ISSN: 0009-9104.
 PUB. COUNTRY: ENGLAND: United Kingdom
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 199908
 ENTRY DATE: Entered STN: 19990827
 Last Updated on STN: 19990827
 Entered Medline: 19990819

AB The immune response of PBMC to gliadin was investigated in patients with coeliac disease (CoD) by examining proliferation, MHC restriction and cytokine production. Gliadin induced low levels of proliferation in 63% of eight untreated patients, 32% of 28 treated patients and 35% of 31 healthy control subjects. In MHC restriction studies, the proliferative response to gliadin was inhibited (range 47-98% inhibition) in the presence of a MoAb to HLA-DR in each of three coeliac and three control donors studied. Using flow cytometry, increased expression of activation markers (HLA-DR and IL-2R) was demonstrated on gliadin-stimulated T cells from four of nine coeliac patients and three of seven healthy control donors. Cytokines were studied in culture supernatants using ELISA. Gliadin was a potent inducer of IL-6 and IL-10 in 100% of coeliac patients and controls, whereas IL-4 was not produced in either subject group. Gliadin induced IL-2 production in 40% of untreated patients, 42% of treated patients and 35% of healthy control donors. Interferon-gamma (IFN-gamma) in gliadin-stimulated cultures was found only in coeliac patients, observed in 33% of untreated patients and 25% of treated patients. Spontaneous secretion of both IL-2 and IFN-gamma was found more frequently in patients with untreated disease (87% of cases versus 21% of controls for IFN-gamma and 40% versus 0% for IL-2). These results suggest, as manifest by IFN-gamma production, that gliadin stimulates a Th1/Th0-like response in coeliac patients and a Th0-like response in healthy controls.

L4 ANSWER 18 OF 79 MEDLINE
 DUPLICATE 8
 ACCESSION NUMBER: 1998435876 MEDLINE
 DOCUMENT NUMBER: 98435876 PubMed ID: 9764847
 TITLE: Interleukin-17 and interferon-gamma synergize in the enhancement of proinflammatory cytokine production by human keratinocytes.
 AUTHOR: Teunissen M B; Koomen C W; de Waal Malefyt R; Wierenga E A; Bos J D
 CORPORATE SOURCE: Department of Dermatology, Academic Medical Center, University of Amsterdam, The Netherlands.
 SOURCE: JOURNAL OF INVESTIGATIVE DERMATOLOGY, (1998 Oct) 111 (4) 645-9.
 Journal code: 0426720. ISSN: 0022-202X.
 PUB. COUNTRY: United States
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals; AIDS
 ENTRY MONTH: 199810
 ENTRY DATE: Entered STN: 19990106

Last Updated on STN: 19990106
 Entered Medline: 19981029

AB Keratinocytes are influenced by cytokines released by skin-infiltrating T lymphocytes. IL-17 is produced by activated CD4+ T cells and can stimulate epithelial cells. We investigated whether IL-17 could modulate the cytokine production and cell-surface molecule expression of keratinocytes. The effects of IL-17 were compared with those of IFN-gamma, which is also derived from activated T cells and is a strong stimulator for keratinocytes. IL-17 enhanced the mRNA and protein production of the proinflammatory cytokines IL-6 and IL-8 in a concentration-dependent way, and induced a weak expression of intercellular adhesion molecule (ICAM)-1 and HLA-DR. The production of IL-1alpha and IL-15 was not altered. IFN-gamma augmented the production of IL-6, IL-8, and IL-15 and strongly induced both cell-surface molecules. IL-17 and IFN-gamma showed marked synergism in the stimulation of IL-6 and IL-8 protein secretion and, to a lesser extent, in the induction of ICAM-1 and HLA-DR expression. The majority of the CD4+ and CD8+ T cell clones derived from lesional psoriatic skin expressed IL-17 mRNA, suggesting that skin-infiltrating T cells can produce this cytokine. This IL-17 mRNA expression was detectable in T helper cell type 1 and type 2 and did not correlate with the IFN-gamma or IL-4 production. In addition, IL-17 mRNA is detectable in biopsies from lesional psoriatic skin, but not in nonlesional control biopsies. Our study indicates that IL-17 is a proinflammatory cytokine, which could amplify the development of cutaneous inflammation and may support the maintenance of chronic dermatoses, through stimulation of keratinocytes to augment their secretion of proinflammatory cytokines.

L4 ANSWER 19 OF 79 CAPLUS COPYRIGHT 2003 ACS
 ACCESSION NUMBER: 1998:523387 CAPLUS
 DOCUMENT NUMBER: 129:244075
 TITLE: Nurse-like cells from bone marrow and synovium of patients with rheumatoid arthritis promote survival and enhance function of human B cells
 AUTHOR(S): Shimaoka, Yasunori; Attrep, Jeanne F.; Hirano, Toshio; Ishihara, Katsuhiko; Suzuki, Ryuji; Toyosaki, Tomoko; Ochi, Takahiro; Lipsky, Peter E.
 CORPORATE SOURCE: Department of Orthopedic Surgery, Osaka University Medical School, Osaka, 565, Japan

SOURCE: Journal of Clinical Investigation
(1998), 102(3), 606-618
CODEN: JCINAO; ISSN: 0021-9738
PUBLISHER: Rockefeller University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Thymic nurse cells are known to interact with T cells and play a role in their functional maturation. However, the role of nurse cells in B cell maturation and differentiation is less well established, esp. at extra-lymphoid sites. To address this issue, nurse-like cell clones from bone marrow and synovial tissue of patients with RA (RA-NLC) were established and characterized. RA-NLC constitutively expressed CD29, CD49c, CD54 (ICAM-1), CD106 (VCAM-1), CD157 (BST-1), and class I MHC mols., and secreted IL-6, IL-7, IL-8, granulocyte-macrophage colony-stimulating factor (GM-CSF) and granulocyte colony-stimulating factor (G-CSF). Bone marrow-derived and synovial RA-NLC differed in that the former secreted IL-7 and expressed a greater d. of CD157 constitutively and after stimulation with IFN.gamma., whereas the latter secreted G-CSF and more IL-6. Stimulation of both bone marrow and synovial RA-NLC induced expression of CD40 and class II MHC, but not CD154 (CD40L) or CD35. RA-NLC rescued peripheral B cells from spontaneous apoptosis and promoted survival of B cells for > 4 wk. B cell survival was blocked by antibodies to CD106 or CD157. RA-NLC also increased Ig prodn. from B cells. After long-term culture (4-6 wk) with RA-NLC, but not alone or with fibroblasts, outgrowth of B cells was obsd. All B cell lines derived from these cultures had been transformed by EBV, although the RA-NLC themselves were not infected with EBV. Precursor frequency anal. indicated that .apprx. 1 in 12,500 peripheral B cells could give rise to these EBV-transformed B cell lines upon coculture with RA-NLC. These results indicate that RA-NLC from bone marrow and synovium have the capacity to rescue B cells from spontaneous apoptosis, facilitate Ig prodn., and promote the outgrowth of EBV-transformed B lymphoblastoid cells. These findings suggest that RA-NLC may play a role in the local and systemic hyperactivity of B cells characteristic of rheumatoid arthritis.

REFERENCE COUNT: 64 THERE ARE 64
CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS
AVAILABLE IN THE RE FORMAT

L4 ANSWER 20 OF 79 MEDLINE
DUPLICATE 9
ACCESSION NUMBER: 1998279289 MEDLINE
DOCUMENT NUMBER: 98279289 PubMed ID:
9616317
TITLE: Protein transport and processing by
human HT29-19A intestinal cells: effect of interferon
gamma.
COMMENT: Comment in: Gut. 1998
Apr;42(4):455-6
AUTHOR: Terpend K; Boisgerault F; Blaton M
A; Desjeux J F; Heyman M
CORPORATE SOURCE: INSERM U290, Hopital St
Lazare, Paris, France.
SOURCE: GUT, (1998 Apr) 42 (4) 538-45.
Journal code: 2985108R. ISSN: 0017-
5749.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL
ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals;
Priority Journals
ENTRY MONTH: 199806
ENTRY DATE: Entered STN: 19980625
Last Updated on STN: 20021217
Entered Medline: 19980616
AB BACKGROUND: The nature of the breakdown
products produced in enterocytes
during epithelial transport of intact proteins may be
critical in
determining the functional consequences of protein
absorption. AIM: (a) To
measure the transepithelial transport of horseradish
peroxidase (HRP) and
to identify the nature of HRP breakdown products
released on the basal
side of enterocytes and (b) to assess the role of
interferon
gamma (IFN gamma) on HRP transport and
processing. METHODS:
HT29-19A intestinal cells were used to assess
transepithelial transport of
HRP in Ussing chambers, and the nature of
breakdown products in the basal
compartment was analysed by high performance
liquid chromatography (HPLC).
RESULTS: (1) In control conditions, [3H]HRP
equivalent fluxes (3135 (219)
ng/h per cm2; mean (SEM) comprised 50% amino
acids, 40% peptides, and 10%
intact HRP. Steric exclusion HPLC of the breakdown
products indicated a
wide range of molecular masses including a major
peptide of about 1150 Da.
Lysosomal aspartyl and thiol proteases were
expressed but no HLA
-DR surface expression was noted, (2) At 48 to 72
hours after
IFN gamma stimulation, [3H]HRP equivalent fluxes
increased significantly
(7392 (1433) ng/h per cm2) without modification of
the relative
proportions of amino acids, peptides, and intact
HRP, and without
modification of the distribution of breakdown
products in HPLC. Lysosomal
protease activities were not modified by IFN gamma
but HLA-

DR expression was increased. CONCLUSION: Intestinal cells are able to process HRP into peptides potentially capable of stimulating the immune system. IFN gamma stimulates the transport and processing of HRP thus increasing the antigenic load in the intestinal mucosa.

L4 ANSWER 21 OF 79 MEDLINE
DUPLICATE 10

ACCESSION NUMBER: 1998432545 MEDLINE
DOCUMENT NUMBER: 98432545 PubMed ID: 9761378

TITLE: Inhibitory effect of pentoxifylline on HLA-DR expression

and glycosaminoglycan synthesis by retrobulbar fibroblasts.

AUTHOR: Balazs C; Kiss H; Farid N R

CORPORATE SOURCE: Ill. Department of Medicine-Endocrinology, Kenezy Teaching Hospital, Debrecen, Hungary.

SOURCE: HORMONE AND METABOLIC RESEARCH, (1998 Aug) 30 (8) 496-9.

Journal code: 0177722. ISSN: 0018-5043.

PUB. COUNTRY: GERMANY: Germany, Federal Republic of

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199812

ENTRY DATE: Entered STN: 19990115

Last Updated on STN: 19990115

Entered Medline: 19981204

AB OBJECTIVE: Glycosaminoglycan (GAG) production by retro-ocular fibroblasts

(REF) is increased in patients with thyroid-associated ophthalmopathy

(TAO). Various cytokines stimulate REFs to proliferate and

elaborate GAG, free oxygen radicals as well as induce HLA-

DR expression on these cells. Pentoxifyllin (Ptx) regulates the

production of several cytokines including tumor necrosis factor alpha

(TNF-alpha), interleukin-1 (IL-1) and, interferon gamma

(IFN-gamma). We wished in this study to determine whether Ptx modified the

spontaneous and cytokine-induced GAG synthesis by REF and IFN-gamma

induced HLA-DR expression. DESIGN: REF derived from

extraocular muscles of healthy subjects were cultured without and with

cytokines (IFN-gamma, TNF alpha and IL-1) and the effect of Ptx on the

production of GAG by REF and HLA-DR expression was

determined. MEASUREMENTS: Glycosaminoglycan was measured by incorporation

of (3H) glycosamine into GAG. HLA-DR expression was

analyzed by fluorescence activated cell sorter.

RESULTS: Both spontaneous

and cytokine induced GAG synthesis by REF was inhibited by Ptx (100, 500

and 1000 mg/l, respectively). IFN-gamma (50, 100 and 500 U/ml) induced a dose-dependent increase in the expression of HLA-DR

molecules by REF. Ptx, which was not toxic to REF, inhibited HLA

-DR expression on those cells dose-dependently.

CONCLUSIONS: Our

in vitro results suggest that Ptx reduces cytokine-induced GAG production

and HLA-DR expression by REF. It thus has

potential as

a therapeutic agent which regulates the function of lymphocytes

infiltrating the retro-orbital tissues, and which are instrumental in TAO.

L4 ANSWER 22 OF 79 CAPLUS COPYRIGHT 2003
ACS

ACCESSION NUMBER: 1997:351412 CAPLUS

DOCUMENT NUMBER: 127:80067

TITLE: Distinct mechanisms of immunosuppression as a

consequence of major surgery

AUTHOR(S): Hensler, Thorsten; Hecker,

Heike; Heeg, Klaus;

Heidecke, Claus-Dieter; Bartels, Holger;

Barthlen,

Winfried; Wagner, Hermann; Siewert,

Jorg-Rudiger;

Holzmann, Bernhard

CORPORATE SOURCE: Department Surgery,

Klinikum rechts der Isar,

Technical University, Munich, D-81675,

Germany

SOURCE: Infection and Immunity (1997), 65(6), 2283-2291

CODEN: INFIBR; ISSN: 0019-9567

PUBLISHER: American Society for

Microbiology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Altered host defense mechanisms after major surgery or trauma are

considered important for the development of infectious complications and

sepsis. In the present study, we demonstrate that major surgery results

in a severe defect of T-lymphocyte proliferation and cytokine secretion in

response to coligation of the antigen receptor complex and CD28. During

the early postoperative course, reduced cytokine secretion was obsd. for

interleukin-2 (IL-2), gamma interferon, and tumor necrosis factor alpha,

which are assocd. with the Th1 phenotype of helper T lymphocytes, and for

IL-4, the index cytokine of Th2 cells. During the late postoperative

course, T-cell cytokine secretion increased to normal levels. Prodn. of

the anti-inflammatory cytokine IL-10 was altered, with different kinetics

being selectively elevated during the late postoperative course. In

contrast, the capacity of peripheral blood monocytes to present bacterial

superantigens and to stimulate T-cell proliferation was normal

or enhanced after surgery despite a significant loss of cell surface HLA-DR mols. Thus, the level of major histocompatibility complex class II protein expression does not appear to predict the antigen-presenting capacity of monocytes obtained from surgical patients with uneventful postoperative recovery. Secretion of IL-1.β and IL-10 by endotoxin-stimulated peripheral blood monocytes was increased at different time points after surgery. Major surgery therefore results in a distinct pattern of immune defects with a predominant defect in the T-cell response to T-cell receptor- and CD28 coreceptor-mediated signals rather than an impaired monocyte antigen-presenting capacity. Suppression of T-cell effector functions during the early phase of the postoperative course may define a state of impaired defense against pathogens and increased susceptibility to infection and septic complications.

L4 ANSWER 23 OF 79 MEDLINE

DUPLICATE 11

ACCESSION NUMBER: 97436557 MEDLINE

DOCUMENT NUMBER: 97436557 PubMed ID: 9292530

TITLE: Myeloma bone marrow plasma cells: evidence for their

capacity as antigen-presenting cells.

AUTHOR: Yi Q; Dabadghao S; Osterborg A;

Bergénbrant S; Holm G

CORPORATE SOURCE: Department of Medicine, Karolinska Hospital, Stockholm, Sweden.

SOURCE: BLOOD, (1997 Sep 1) 90 (5) 1960-7.

Journal code: 7603509. ISSN: 0006-4971.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals

ENTRY MONTH: 199709

ENTRY DATE: Entered STN: 19971013

Last Updated on STN: 20021218

Entered Medline: 19970930

AB Myeloma plasma cells constitute 10% to 90% of the total bone marrow cell count in patients with multiple myeloma (MM). These cells express a variety of cell surface markers, such as HLA-ABC and HLA-

DR, and surface antigens that are necessary for professional antigen-presenting cells, including adhesion and costimulatory molecules.

In this study, we examined the expression of major histocompatibility complex (MHC) and costimulatory molecules on CD38(bright,++) plasma cells

in bone marrow aspirates from eight MM patients.

Small percentages of plasma cells expressed weak but detectable levels of HLA-

DR, HLA-DQ, CD40, CD80, and CD86, which could be upregulated by interferon-gamma (IFN-γ) and tumor necrosis factor-α. CD38++ plasma cell and CD38(dim,+) cells were sorted from freshly isolated bone marrow mononuclear cells and tested for their capacity to act as antigen-presenting cells. Indeed, both CD38++ plasma cells and CD38+ cells were able to stimulate allogeneic T cells and present the soluble antigens purified protein derivative and tetanus toxoid to autologous T cells. Recognition of the antigens led to T-cell proliferation and secretion of IFN-γ and was MHC class-I and -II restricted. Antigen processing and presentation by CD38++ and CD38+ cells were abolished by treatment of the cells with chloroquine. Hence, our study provides for the first time evidence that myeloma plasma cells may act as antigen-presenting cells. Further studies are warranted to examine in detail the molecules required for inducing T-cell stimulation.

L4 ANSWER 24 OF 79 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1997:365639 CAPLUS

DOCUMENT NUMBER: 127:60351

TITLE: Beta-sitosterol and beta-sitosterol glucoside

stimulate human peripheral blood

lymphocyte

proliferation: implications for their use

as an

immunomodulatory vitamin combination

AUTHOR(S): Bouic, P. J. D.; Etsebeth, S.;

Liebenberg, R. W.;

Albrecht, C. F.; Pegel, K.; Van

Jaarsveld, P. P.

CORPORATE SOURCE: Departments of Medical Microbiology and Pharmacology,

Faculty of Medicine, University of

Stellenbosch,

Tygerberg, 7505, S. Afr.

SOURCE: International Journal of

Immunopharmacology (1997),

Volume Date 1996, 18(12), 693-700

CODEN: IJIMDS; ISSN: 0192-0561

PUBLISHER: Elsevier

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The phytosterols, β-sitosterol (BSS), and its glucoside (BSSG)

enhance the in vitro proliferative response of T-cells stimulated by

sub-optimal concns. of phytohemagglutinin (PHA) several fold at extremely

low concns. (femtogram level). A 100:1

(mass:mass) ratio of BSS:BSSG

(termed essential sterolin formulation, ESF) showed higher stimulation

than the individual sterols at the same concn. In

in vivo activity of ESF

was also demonstrated when volunteers ingested ESF for 4 wk.

Proliferation of their T-cells, stimulated maximally with PHA, was significantly enhanced (20-920%) when compared to baseline values. In vitro, ESF (1 .mu.g/mL) was able to significantly enhance the expression of CD25 and HLA-Dr activation antigens on T-cells and increased the secretion, into the medium, of IL-2 and gamma interferon. NK-cell activity was also increased by BSS and BSSG alone, but with ESF a higher activity was always found at different effector:target ratios (100:1-12:1).

L4 ANSWER 25 OF 79 MEDLINE

DUPLICATE 12

ACCESSION NUMBER: 97319193 MEDLINE

DOCUMENT NUMBER: 97319193 PubMed ID: 9176096

TITLE: T-cell cytokines may control the balance of functionally distinct macrophage populations.

AUTHOR: Tormey V J; Faul J; Leonard C; Burke C M; Dilmecc A; Poultier L W

CORPORATE SOURCE: Department of Clinical Immunology, Royal Free Hospital School of Medicine, London, UK.

SOURCE: IMMUNOLOGY, (1997 Apr) 90 (4) 463-9.

Journal code: 0374672. ISSN: 0019-2805.

PUB. COUNTRY: ENGLAND: United Kingdom

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals; AIDS

ENTRY MONTH: 199706

ENTRY DATE: Entered STN: 19970709

Last Updated on STN: 19970709

Entered Medline: 19970623

AB As monocytes differentiate into mature macrophages, subsets emerge that exhibit stimulatory, suppressive or phagocytic potential. These functionally distinct subsets can be discriminated using monoclonal antibodies RFD1 and RFD7. As examples of all these subsets have been repeatedly identified within the macrophage pool in a variety of organs the overall functional capacity of this pool will depend on the relative balance of these subpopulations. This study investigates whether this balance present in mature macrophage populations can be regulated by the local influence of T-cell-derived cytokines. The dose-dependent effect of cytokines interferon-gamma (IFN-gamma), interleukins (IL) IL-2, IL-4 and IL-10 on the phenotype and function of monocyte-derived macrophages was determined. Subsets of mature cells were quantified by identifying RFD1- RFD7- stimulatory cells (D1+); RFD1- RFD7+ phagocytes (D7+) and RFD1+ RFD7+ suppressive cells (D1 D7+). IFN-gamma and

IL-4 increased the relative proportions of D1+ stimulatory cells and upregulated HLA-DR expression. IFN-gamma also increased the capacity of the mature macrophage pool to stimulate T-cell proliferation. IL-10 reduced the proportions of D1+ stimulatory cells while promoting the differentiation of D7+ phagocytes and D1/D7+ suppressive cells. IL-10 induced changes also reduced the functional capacity of the mature populations to stimulate T cells in auto and allogenic mixed lymphocyte reactions (MLR). IL-2 had no effect on differentiation of monocytes. Thus IL-4 and IFN-gamma are seen to induce the development of stimulatory macrophages while IL-10 promotes differentiation of monocytes to mature phagocytes and suppressive macrophages. It is concluded that mature macrophage phenotype is 'plastic' and under the control of T-cell-derived mediators. Furthermore, within the differentiating monocytes, phenotypic change appears to carry with it functional change, thus retaining the relationship between antigen expression and activity in the mature macrophage populations.

L4 ANSWER 26 OF 79 MEDLINE

DUPLICATE 13

ACCESSION NUMBER: 97471725 MEDLINE

DOCUMENT NUMBER: 97471725 PubMed ID: 9330666

TITLE: Inhibitory effect of pentoxifylline on HLA-DR expression

and glycosaminoglycan synthesis of retrobulbar fibroblasts

induced by interferon gamma.

AUTHOR: Balazs C; Kiss E; Farid N R

CORPORATE SOURCE: III. Department of Medicine-Endocrinology, Kenezy Teaching Hospital, Debrecen, Hungary.

SOURCE: ACTA MICROBIOLOGICA ET IMMUNOLOGICA HUNGARICA, (1997) 44

(2) 173-9.

Journal code: 9434021. ISSN: 1217-8950.

PUB. COUNTRY: Hungary

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199711

ENTRY DATE: Entered STN: 19971224

Last Updated on STN: 19971224

Entered Medline: 19971113

AB Glycosaminoglycan (GAG) accumulation produced by retroocular fibroblasts (REF) has been observed in patients with thyroid-associated ophthalmopathy (TAO). Various cytokines are able to express HLA-DR molecules and stimulate the REF to proliferate GAG and free oxygen radicals. Pentoxifylline (Ptx) is known to have complex

immunomodulatory effects on production of cytokines including interferon gamma (IFN-gamma). Ptx has been assumed to inhibit the cytokine-induced production of GAG and HLA-DR expression. We wished to determine whether Ptx has an effect on the IFN-gamma induced HLA-DR expression and influences the spontaneous and cytokine-induced GAG synthesis of REF. REF derived from extraocular muscles of healthy subjects were cultured without and with IFN-gamma. The effect of Ptx on expression of HLA-DR molecules and the production of GAG by REF was determined. Glycosaminoglycan was measured by incorporation of (3H)glycosamine into GAG. HLA-DR expression was analysed by fluorescence activated cell sorter. IFN-gamma (50, 100 and 500 U/ml) induced an increase in expression of HLA-DR molecules of REF. Ptx was proved not to be toxic for cultured cells. This drug was able to dose-dependently inhibit HLA-DR expression of REF. Both spontaneous and IFN-gamma-induced GAG synthesis of REF was inhibited by Ptx (100, 500 and 1000 mg/l, respectively). Due to in vitro inhibitory effects, Ptx is potentially able to modify the antigen presentation and the GAG synthesis by REF and it might be a useful therapeutical drug in the treatment of TAO.

L4 ANSWER 27 OF 79 MEDLINE
DUPLICATE 14

ACCESSION NUMBER: 97222552 MEDLINE
DOCUMENT NUMBER: 97222552 PubMed ID:
9069581

TITLE: Differential effects of human interferon
alpha and

interferon gamma on xenografted human
thyroid tissue in severe combined
immunodeficient mice and
nude mice.

AUTHOR: Kawai K; Enomoto T; Fornasier V;
Resetskova E; Volpe R

CORPORATE SOURCE: Endocrinology Research
Laboratory, Wellesley Hospital,
University of Toronto, Ontario, Canada.

SOURCE: PROCEEDINGS OF THE
ASSOCIATION OF AMERICAN PHYSICIANS,
(1997 Mar) 109 (2) 126-35.

Journal code: 9514310. ISSN: 1081-650X.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL
ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199706

ENTRY DATE: Entered STN: 19970612

Last Updated on STN: 20000303

Entered Medline: 19970603

AB We have studied the in vivo effects of human
interferon alpha (IFN-alpha)
and interferon gamma (IFN-gamma) administration
on

human thyroid tissue xenografted into two mouse
strains: severe combined
immunodeficient (SCID) mice and nude mice.

Human lymphocytes survive in

SCID mice but are lysed in nude mice. Thyroid

tissues from Graves' disease

or Hashimoto's thyroiditis, or paranodular [normal,

(N)] tissue was

xenografted into SCID mice (0.8 g/mouse)

pretreated with anti-asialo GM-1

antisera and radiation and also into nude mice.

One week after

xenografting, SCID and nude mice were divided into

three groups. Group A

was treated with IFN-alpha intraperitoneally (2,000
units/mouse) three

times weekly; group B was treated with IFN-gamma

similarly; group C was

treated with phosphate buffered saline (PBS) only

(control). Autologous

human peripheral blood mononuclear cells (PBMCs)

were added to mice

receiving N xenografts. Blood was taken every 2

weeks for levels of IgG

and thyroid antibodies (TAB). After 6 weeks of

treatment, mice were

sacrificed, and xenograft thyrocyte histocompatibility

leukocyte antigen (

HLA-DR) and intercellular adhesion molecule

(ICAM-1)

expression were measured. In addition, thyrocyte

cultures were stimulated

in vitro with 200 units/ml of either IFN-alpha or IFN-

gamma or PBS

(control). SCID mice xenografted with autoimmune

thyroid disease (AITD) in

group A showed a significantly higher TAB

production than group C, whereas

in group B, TAB production was not statistically

increased compared to

control (group C). SCID mice xenografted with N did

not produce TAB in any

group, nor did nude mice xenografted with AITD.

Thyrocyte HLA-

DR expression was markedly increased in group A

and B in SCID mice

xenografted with Graves' disease, Hashimoto's

thyroiditis, and N tissue

compared to group C. In contrast, only group B (IFN-

gamma) showed an

increase in thyrocyte HLA-DR in nude mice. In the in

vitro studies, only IFN-gamma (not IFN-alpha)

stimulated thyrocyte

HLA-DR and ICAM-1 expression in Graves' disease,

Hashimoto's thyroiditis, and N tissues. We

concluded that in SCID mice,

IFN-alpha causes TAB production in AITD

xenografts but not in N

xenografts, while increasing thyrocyte HLA-DR

expression in both. Also, IFN-gamma does not

cause a statistically

increased TAB in AITD xenografts in SCID mice,

despite a sharp rise in

thyrocyte HLA-DR expression. In addition, because

IFN-alpha has no effect in nude mice or in vitro on

thyrocyte HLA

-DR expression, its effects in SCID mice must be mediated via local infiltrating lymphocytes. Finally, IFN-gamma has a direct effect on thyrocytes to increase HLA-DR expression (and, in vitro, ICAM-1 expression) but may not stimulate TAb production.

L4 ANSWER 28 OF 79 MEDLINE

DUPLICATE 15

ACCESSION NUMBER: 97174265 MEDLINE
DOCUMENT NUMBER: 97174265 PubMed ID:
9021999

TITLE: Antigen presentation by interferon-gamma

-treated thyroid follicular cells inhibits interleukin-2 (IL-2) and supports IL-4 production by B7-dependent human T cells.

AUTHOR: Lombardi G; Arnold K; Uren J; Marelli-Berg F; Hargreaves R;

Imami N; Weetman A; Lechler R

CORPORATE SOURCE: Department of Immunology, Royal Postgraduate Medical School, London, GB..

glombard@rpms.ac.uk

SOURCE: EUROPEAN JOURNAL OF IMMUNOLOGY, (1997 Jan) 27 (1) 62-71.

Journal code: 1273201. ISSN: 0014-2980.

PUB. COUNTRY: GERMANY: Germany, Federal Republic of

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals; AIDS

ENTRY MONTH: 199703

ENTRY DATE: Entered STN: 19970313

Last Updated on STN: 19970313

Entered Medline: 19970305

AB The consequence of recognition of antigen on antigen-presenting cells that are induced to express major histocompatibility complex (MHC) class II molecules following an inflammatory process is still not clear. In this study, we have investigated the outcome of antigen presentation by epithelial cells and we have used as a model thyroid follicular cells (TFC) that are known to express MHC class II molecules in autoimmune thyroid diseases and acquire the capacity to present autoantigens to T cells infiltrating the thyroid gland. The result show that MHC class II-expressing TFC were unable to stimulate a primary T cell alloresponse, using CD4+ T cells from three HLA-mismatched responders. Phenotypic analysis showed that TFC, after incubation with interferon-gamma, do not express the costimulatory molecules B7-1 (CD80) and -2 (CD86). Addition of murine DAP.3 cells expressing human B7-1 (DAP.3-B7) to cultures containing peripheral blood CD4+ T cells and DR1-expressing TFC led to a proliferative response,

suggesting that the failure of TFC to stimulate a primary

alloresponse was due to a lack of co-stimulation. Similarly, HLA

-DR-restricted, influenza-specific T cell clones dependent on B7

for co-stimulation did not respond to peptide

presented by TFC; again the

lack of response could be overcome by co-culture of TFC with DAP.3-B7.

Furthermore, recognition of antigen on TFC inhibited interleukin-2 (IL-2)

production in the B7-dependent T cells. In contrast, in T helper type 0

(Th0) T cells, IL-4 release was not affected by TFC presentation. In

addition, antigen presentation by TFC favored IL-4 production relative to

IL-2 production by B7-independent Th0 clones.

These results suggest that

antigen presentation by MHC class II+ TFC may induce tolerance in

autoreactive Th1 cells but may simultaneously favors a Th2 response in

uncommitted T cells, and thereby support autoantibody production.

L4 ANSWER 29 OF 79 MEDLINE

DUPLICATE 16

ACCESSION NUMBER: 97083790 MEDLINE

DOCUMENT NUMBER: 97083790 PubMed ID:
8930134

TITLE: Transforming growth factor-beta inhibits interferon

-gamma-induced HLA-DR expression by cultured

human fibroblasts.

AUTHOR: Armendariz-Borunda J; Endres R O; Ballou L R; Postlethwaite

A E

CORPORATE SOURCE: Institute of Molecular Biology in Medicine, CUCS,

University of Guadalajara, Jal, Mexico.

SOURCE: INTERNATIONAL JOURNAL OF BIOCHEMISTRY AND CELL BIOLOGY, .

(1996 Oct) 28 (10) 1107-16.

Journal code: 9508482. ISSN: 1357-2725.

PUB. COUNTRY: ENGLAND: United Kingdom

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199612

ENTRY DATE: Entered STN: 19970128

Last Updated on STN: 19970128

Entered Medline: 19961231

AB This study shows the induction of HLA-DR (DR) in fibroblasts by IFN-gamma and investigates the molecular mechanisms involved in the further DR down-regulation by TGF-beta 1. Kinetics of DR induction on human dermal fibroblasts by IFN-gamma showed that 1 hr of exposure was required to induce detectable levels of DR, and maximal DR expression was achieved only after 2 days of exposure to IFN-gamma.

TGF-beta 1 inhibited DR induction by IFN-gamma, although complete

inhibition never could be achieved, even with high concentrations of TGF-beta 1 and low concentrations of IFN-gamma. Inhibition was not accounted for by reduction in cell numbers, as TGF-beta 1 stimulated growth of the fibroblasts. Inhibition of DR induction was seen only if TGF-beta 1 was added during the first 24 hr of IFN-gamma treatment. TGF-beta 1 inhibited equally well if the cells were pretreated for as little as 1 hr and then washed before addition of IFN-gamma. TGF-beta 1 did not cause an overall suppression of protein synthesis. Northern blot analysis revealed that TGF-beta 1 greatly reduced the steady-state level of DR beta mRNA induced by IFN-gamma at 24 hr, and then DRP transcripts became undetectable at later stages. It is concluded that early intracellular signals must build up to stimulate maximum DR synthesis, which, later on, are inactivated or degraded by the action of TGF-beta 1. We suggest that these mechanisms regulating DR gene transcription involve the action of genes coding for specific IFN-gamma-inducible transcriptional factors that are turned on and off in an expeditious manner.

L4 ANSWER 30 OF 79 MEDLINE
 DUPLICATE 17
 ACCESSION NUMBER: 97081846 MEDLINE
 DOCUMENT NUMBER: 97081846 PubMed ID: 8923089
 TITLE: Current and future clinical applications of interferon-gamma in host antimicrobial defense.
 AUTHOR: Murray H W
 CORPORATE SOURCE: Department of Medicine, Cornell University Medical College, New York, NY 10021, USA.
 CONTRACT NUMBER: AI 16963 (NIAID)
 SOURCE: INTENSIVE CARE MEDICINE, (1996 Oct) 22 Suppl 4 S456-61.
 Ref: 21
 Journal code: 7704851. ISSN: 0342-4642.
 PUB. COUNTRY: United States
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 General Review; (REVIEW) (REVIEW, TUTORIAL)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals; AIDS
 ENTRY MONTH: 199702
 ENTRY DATE: Entered STN: 19970305
 Last Updated on STN: 19970305
 Entered Medline: 19970214
 AB The T cell-derived macrophage-activating lymphokine, interferon-gamma (IFN-gamma), is the most broadly acting antimicrobial-inducing and host defense-enhancing cytokine thus far identified in

experimental models of infectious diseases. The activity induced by IFN-gamma encompasses all classes of non-viral pathogens including intracellular and extracellular parasites, fungi and bacteria. In man, treatment with immuno-enhancing doses of IFN-gamma is safe, well-tolerated and stimulates the antimicrobial mechanisms of blood monocytes, circulating neutrophils and tissue macrophages. Aerosol administration activates alveolar macrophages in a compartmentalized fashion. Monocytes from IFN-gamma-treated patients with cancer, leprosy, and AIDS all respond with the activated phenotype, and suppressed monocyte HLA-DR expression in trauma patients can be up-regulated by IFN-gamma therapy. Thus far, IFN-gamma has been recognized as effective in the prophylaxis of chronic granulomatous disease and as adjunctive treatment in at least one systemic intracellular infection, visceral leishmaniasis. Additional trials suggest beneficial effects as prophylaxis in trauma and as treatment in leprosy, cutaneous leishmaniasis, and HIV- and non-HIV-related disseminated atypical mycobacterial infection. IFN-gamma is also being tested as a prophylaxis in patients with burns and advanced HIV infection and as an adjunct in drug-resistant tuberculosis. Future antimicrobial applications for IFN-gamma include: a) long-term prophylaxis in T cell-deficient states, b) short-term prophylaxis in patients with a reversible host defense defect such as granulocytopenia or immune response suppression induced by trauma or burn injury, and c) adjunctive treatment along with conventional antibiotic therapy for i) nosocomial pneumonia (aerosol administration), ii) opportunistic infections in general, iii) infections which typically respond poorly to available treatment and iv) for infections which require prolonged therapy for cure. In the latter, the addition of IFN-gamma may accelerate the response to conventional therapy and permit a clinically important reduction in the duration of treatment while preserving efficacy.

L4 ANSWER 31 OF 79 MEDLINE
 DUPLICATE 18
 ACCESSION NUMBER: 96370466 MEDLINE
 DOCUMENT NUMBER: 96370466 PubMed ID: 8774362
 TITLE: Staphylococcal enterotoxin B-specific adhesion of murine splenic T cells to a human endothelial cell line.
 AUTHOR: Kita M; Eguchi K; Kawabe Y; Tsukada T; Migita K; Kawakami A; Matsuoka N; Nagataki S

CORPORATE SOURCE: First Department of Internal
Medicine, Nagasaki University
School of Medicine, Japan.

SOURCE: IMMUNOLOGY, (1996 Jul) 88 (3)
441-6.

Journal code: 0374672. ISSN: 0019-2805.

PUB. COUNTRY: ENGLAND: United Kingdom

DOCUMENT TYPE: Journal; Article; (JOURNAL
ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199610

ENTRY DATE: Entered STN: 19961015

Last Updated on STN: 19961015

Entered Medline: 19961002

AB The presence of a putative autoantigen of
autoimmune disorder in a target
organ may cause accumulation of specific T cells in
the inflammatory
region. One of the mechanisms of such
accumulation involves the migration
of specific-circulating T cells through the endothelial
cells into the
target lesion. The presence of only a few specific T
cells responsive to a
putative autoantigen has hampered the investigation
of specific migration
of circulating T cells to the target organ. We used a
superantigen to
investigate specific T-cell adhesion to endothelial
cells, because it
stimulates a large proportion of T cells with particular
V beta
elements and adhesion of T cells to the endothelium
is a vital step in the
migration process. Adhesion of murine T cells to the
human endothelial
cell line, EA.hy926, was specifically increased in the
presence of
staphylococcal enterotoxin B (SEB). The increase
was interferon-
gamma (IFN-gamma)-dependent, and consisted
mainly of CD4+ T cells.
V beta 8.1,2+ T cells preferentially adhered to
endothelial cells in the
presence of SEB compared with V beta 6+ T cells.
Pretreatment of
endothelial cells with SEB increased the adherence
of V beta 8.1,2+ T
cells, while anti-human leucocyte antigen (HLA)-DR
and
-DQ antibodies inhibited the increased adherence of
V beta 8.1,2+ T cells.
Our results demonstrate that increased T-cell
adhesion to endothelial
cells is SEB specific, and that the specificity is
dependent on major
histocompatibility complex (MHC) class II molecules
expressed on
endothelial cells and on the recognition of the SEB-
MHC class II complex
by V beta 8.1,2+ T cells.

L4 ANSWER 32 OF 79 MEDLINE

DUPLICATE 19

ACCESSION NUMBER: 96180265 MEDLINE

DOCUMENT NUMBER: 96180265 PubMed ID:
8599973

TITLE: Constitutive production of colony-
stimulating factors by

human hepatoma cell lines: possible
correlation with cell
differentiation.

AUTHOR: Wang S Y; Chen L Y; Tsai T F; Su T
S; Choo K B; Ho C K

CORPORATE SOURCE: Department of Medical
Research, Veterans General
Hospital-Taipei, Taiwan, Republic of China.

SOURCE: EXPERIMENTAL HEMATOLOGY,
(1996 Feb) 24 (3) 437-44.

Journal code: 0402313. ISSN: 0301-472X.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL
ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199604

ENTRY DATE: Entered STN: 19960513

Last Updated on STN: 19970203

Entered Medline: 19960426

AB A panel of two poorly differentiated (HA22T/VGH
and SK-Hep-1) and six
well-differentiated (HuH-6-cl 5, HuH-7, PLC/PRF/5,
Hep G2, Hep 3B, and
Tong) human hepatocellular carcinoma (HCC) cell
lines were studied for the
production of colony-stimulating factors (CSFs)
using the granulocyte and
macrophage colony formation (CFU-GM) assay,
immunocytochemical staining,
and Northern blotting. Medium conditioned by
untreated HA22T/VGH cells
contained a high level of CSFs that could stimulate
the in vitro
colony formation of human myeloid progenitor cells.
The HA22T/VGH
cell-derived CSF had an apparent molecular weight
of 23 kD. Its activity
could be effectively neutralized by antiserum against
granulocyte-
macrophage CSF (GM-CSF) but not by antibodies to
other hematopoietic
growth factors, including G-CSF, M-CSF, interleukin-
3 (IL-3), and IL-6.
Correspondingly, immunocytochemical studies using
monoclonal anti-GM-CSF
showed a strong positive reaction in the cytoplasm
of the HA22T/VGH cells.
Northern blot analysis revealed that untreated
HA22T/VGH cells expressed a
considerable amount of GM-CSF mRNA, confirming
that GM-CSF production was
constitutive. At optimal concentrations,
lipopolysaccharide (LPS),
IL-1beta, interferon-gamma (IFN-gamma), and
tumor-promoting phorbol diester (TPA) could all
stimulate
HA22T/VGH cells to secrete GM-CSF. In addition to
HA22T/VGH, SK-Hep-1
cells could also produce GM-CSF, although less
effectively, whereas all
the well-differentiated HCC cell lines tested were
negative for CSF
production. Morphologic, cytochemical, and
immunocytochemical examinations
demonstrated that both poorly differentiated CSF-
producing HCC cell lines
(HA22T/VGH and SK-Hep-1) were macrophage-like
in morphology, possessed

nonspecific esterase (NSE) activity, and expressed CD14, CD68, and HLA-DR on their surface, while all the well-differentiated HCC cell lines were epithelioid and lacked myeloid differentiation antigens. These results suggest that monocytoïd features and CSF production may be differentiation markers of hepatocytes at the immature stages, and that the HA22T/VGH and SK-Hep-1 cell lines may be valuable tools for the study of hepatic function and differentiation.

L4 ANSWER 33 OF 79 MEDLINE

DUPLICATE 20

ACCESSION NUMBER: 97180617 MEDLINE

DOCUMENT NUMBER: 97180617 PubMed ID: 9028793

TITLE: Human keratinocytes constitutively express IL-4 receptor

molecules and respond to IL-4 with an increase in B7/BB1 expression.

AUTHOR: Junghans V; Jung T; Neumann C
CORPORATE SOURCE: Department of Dermatology, University of Gottingen, Germany.

SOURCE: EXPERIMENTAL DERMATOLOGY, (1996 Dec) 5 (6) 316-24.

Journal code: 9301549. ISSN: 0906-6705.

PUB. COUNTRY: Denmark

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199706

ENTRY DATE: Entered STN: 19970630

Last Updated on STN: 19980206

Entered Medline: 19970619

AB In certain pathological conditions, such as atopic dermatitis, interleukin-4 (IL-4) can be detected in the skin. As the role of this cytokine in inflammatory skin lesions is not completely clear, we investigated its biological effects on skin keratinocytes. It was found that freshly isolated as well as cultured keratinocytes obtained from normal individuals express mRNA for the IL-4 receptor (IL-4R) and produce IL-4R protein, as determined by flow cytometry. Moreover, IL-4 induced a proliferative response in keratinocytes after 1 day of culture and enhanced B7/BB1 expression in these cells. B7-2 (CD86) mRNA and protein were neither detected on untreated nor IL-4 treated keratinocytes. In contrast to interferon-gamma (IFN-gamma), IL-4 did not induce ICAM-1 (CD54) or HLA-DR-expression. Keratinocytes which had been treated with IL-4 showed an enhanced ability to stimulate allogeneic T-cell proliferation in the presence of staphylococcus enterotoxin B (SEB), ($p < 0.01$). Neutralizing anti-B7/BB1

monoclonal antibodies did not block this effect.

These results indicate

that other molecules than B7/BB-1. HLA-DR or ICAM-1 on

IL-4-activated keratinocytes may be involved in T-cell stimulation. In

conclusion our results suggest that locally produced IL-4, besides

modulating keratinocyte membrane molecules, may enable keratinocytes to

interact with skin infiltrating lymphocytes.

L4 ANSWER 34 OF 79 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1996:626195 CAPLUS

DOCUMENT NUMBER: 125:273544

TITLE: Alloproliferation of purified CD4+ T cells to adult

human heart endothelial cells, and

study of

second-signal requirements

AUTHOR(S): McDouall, R. M.; Page, C. S.; Hafizi, S.; Yacoub, M.

H.; Rose, M. L.

CORPORATE SOURCE: National Heart Lung Inst. (Imperial College),

Harefield Hosp., Middlesex, UK

SOURCE: Immunology (1996), 89(2), 220-226

CODEN: IMMUAM; ISSN: 0019-2805

PUBLISHER: Blackwell

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Human endothelial cells have been shown to be capable of causing direct

allostimulation of T cells. However, the majority of immunol. studies of

human endothelial cells have been performed on cells of fetal origin.

Here we use endothelial cells isolated from the adult human heart, both

large vessel (coronary artery, pulmonary artery and aorta) and also

microvascular. We have examd. the ability of all these endothelial cells

to cause direct allostimulation of T cells, and show that purified CD4+ T

cells can proliferate in response to adult human heart endothelial cells,

the response being dependent on pretreatment of the endothelial cells with

interferon-gamma. (IFN-gamma.) and inhibited by anti-HLA-DR monoclonal antibody. The proliferative

responses of CD8+ T

cells to adult but not fetal endothelial cells was inconsistent and weak.

Proliferative responses were not blocked by CTLA4-Ig, which inhibits

T-cell responses to 'classical' antigen-presenting cells (APC), but >50%

inhibition was achieved with monoclonal antibody to lymphocyte

function-assocd. antigen-3 (LFA-3). These results show that adult human

cardiovascular endothelial cells are capable of causing allostimulation of

resting CD4+ T cells, using a different second signal to classical APC.

In view of these findings, endothelial cells should be considered as APC

following solid organ transplantation.

L4 ANSWER 35 OF 79 MEDLINE

DUPLICATE 21

ACCESSION NUMBER: 96409610 MEDLINE

DOCUMENT NUMBER: 96409610 PubMed ID:

8814591

TITLE: Antigen-presenting-cell function of
interferon

gamma-treated human gingival fibroblasts.

AUTHOR: Shimabukuro Y; Murakami S; Okada
H

CORPORATE SOURCE: Department of
Periodontology and Endodontology, Osaka
University Faculty of Dentistry, Japan.

SOURCE: JOURNAL OF PERIODONTAL

RESEARCH, (1996 Apr) 31 (3) 217-28.

Journal code: 0055107. ISSN: 0022-3484.

PUB. COUNTRY: Denmark

DOCUMENT TYPE: Journal; Article; (JOURNAL
ARTICLE)

LANGUAGE: English

FILE SEGMENT: Dental Journals; Priority Journals

ENTRY MONTH: 199611

ENTRY DATE: Entered STN: 19961219

Last Updated on STN: 19961219

Entered Medline: 19961120

AB The present study was carried out to examine the
antigen-presenting cell
(APC) functions of human gingival fibroblasts (HGF)
elicited with IFN

gamma. Stimulation of HGF with IFN gamma clearly
induced HLA-

DR expression and enhanced expression of
intercellular adhesion

molecule-1 (ICAM-1) on HGF. Despite the
phenotypical resemblance of IFN

gamma-treated HGF to so-called APC, HLA-DR
positive

HGF were unable to induce proliferation of allo-
reactive peripheral blood

T cells (PBT) isolated from different donors. The
failure of IFN

gamma-treated HGF to stimulate unprimed allo-
reactive PBT was

not due to the lack of production of IL-1 or the
immunosuppressive effect

of PGE2 from HGF. On the other hand, the fact that
detectable expression

of CD80, ligand for CD28, was not found on IFN
gamma-treated HGF may at

least in part explain the ineffective function of HGF
as APC.

Interestingly, IFN gamma-treated HGF induced
proliferation of primed

allo-reactive CD4+ T cells in a HLA-DR dependent
manner, suggesting that IFN gamma-treated HGF

may have the ability to
stimulate pre-activated T cells. We then confirmed

that high
levels of IFN gamma mRNA were detectable in

inflamed gingival tissue.

Although it cannot be concluded from this study that
HGF are incapable of

effectively presenting antigenic peptides to
autologous T cells bearing

appropriate T cell receptors, present results suggest
that HGF may be

affected by locally-secreted IFN gamma and that the
IFN gamma-stimulated

HGF may play a role in regulating immune
responsiveness in inflammatory
periodontal lesions.

L4 ANSWER 36 OF 79 MEDLINE

DUPLICATE 22

ACCESSION NUMBER: 96348748 MEDLINE

DOCUMENT NUMBER: 96348748 PubMed ID:
8725884

TITLE: Dual expression of human leukocyte
antigen molecules and
the B7-1 costimulatory molecule (CD80) on
human melanoma

cells after particle-mediated gene transfer.

AUTHOR: Albertini M R; Emler C A; Schell K;
Tans K J; King D M;

Sheehy M J

CORPORATE SOURCE: University of Wisconsin
Comprehensive Cancer Center,
Madison, USA.

CONTRACT NUMBER: 3-MO1-RR03186-0782
(NCRR)

CA 68466-02 (NCI)

SOURCE: CANCER GENE THERAPY, (1996
May-Jun) 3 (3) 192-201.

Journal code: 9432230. ISSN: 0929-1903.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL
ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199611

ENTRY DATE: Entered STN: 19961219

Last Updated on STN: 19980206

Entered Medline: 19961108

AB The aim of this study was to determine if human
melanoma cells could be

molecularly modified by particle-mediated gene
transfer with a "gene gun",

using genes for interferon-gamma (IFN-gamma), the
B7-1

costimulatory molecule (CD80), and human
leukocyte antigen (HLA)-A2, to

augment expression of both HLA molecules and B7-
1. Established and early

passage melanoma cells transfected with human
IFN-gamma complementary DNA

(cDNA) produced IFN-gamma (50-5,000 pg/mL).

The biological effect of this

IFN-gamma transgene included an upregulation, or
de novo appearance, of

HLA expression. These melanoma cells had no
detectable baseline surface

expression of the B7-1 costimulatory molecule, but
8% to 31% of these

cells became B7-1 positive with no selection
procedure after gene transfer

with human B7-1 cDNA. After combination gene
transfer with cDNAs for both

IFN-gamma and B7-1, 9% to 33% of these cells
expressed both HLA-

DR and B7-1. In combination gene transfer
experiments with cDNAs

for both HLA-A2 and B7-1, dual expression of HLA-
A2 and B7-1 was achieved

in 10% to 17% of the melanoma cells. Thus, the
molecular modification of

human melanoma cells to increase expression of
both HLA and B7-1 can be

achieved by particle-mediated gene delivery and presents a promising strategy to stimulate antimelanoma T-cell immunity.
Key words:
Melanoma; T cells; B7-1 costimulatory molecule (CD80); major histocompatibility complex.

L4 ANSWER 37 OF 79 MEDLINE

DUPLICATE 23

ACCESSION NUMBER: 97177474 MEDLINE

DOCUMENT NUMBER: 97177474 PubMed ID: 9024990

TITLE: Synergistic effect of prolactin on IFN-gamma-mediated

growth arrest in human monoblastic cells: correlation with

the up-regulation of IFN-gamma receptor gene expression.

AUTHOR: Sedo A; Van Weyenbergh J;

Rouillard D; Bauvois B

CORPORATE SOURCE: Unite 365 INSERM Institut Curie, Paris, France.

SOURCE: IMMUNOLOGY LETTERS, (1996 Nov) 53 (2-3) 125-30.

Journal code: 7910006. ISSN: 0165-2478.

PUB. COUNTRY: Netherlands

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199705

ENTRY DATE: Entered STN: 19970523

Last Updated on STN: 19970523

Entered Medline: 19970512

AB Interferon-gamma (IFN-gamma) stimulates the development of monocytic features in human myeloid precursors. Because transcriptional regulation of IFN-gamma and the pituitary hormone prolactin (PRL) has been described to involve common Jak-STAT pathways, we addressed here the question of whether PRL plays a role in monoblastic (U937) cell growth and macrophage maturation. In contrast to IFN-gamma, PRL did not affect U937 cell growth nor induction of differentiation as assessed by the unchanged cell surface expression of maturation markers CD11b and HLA-DR class II. However, PRL in synergy with IFN-gamma inhibited, in a time- and dose-dependence, proliferation of U937 cells without influencing their maturation induced by IFN-gamma. IFN-gamma and PRL both affected the expression of the IFN-gamma receptor (IFN-gamma R) gene by increasing IFN-gamma R mRNA levels. The rise in IFN-gamma R transcripts was accompanied by a low but significant release of IL-6 which has previously been shown to stabilize IFN-gamma R mRNA. Moreover, a transient increase in surface expression of IFN-gamma R was observed in U937 cells treated by IFN-gamma alone or in combination with PRL, whereas no apparent modulation of cell surface IFN-gamma R was

observed in cells treated with PRL. Lastly, PRL did not induce transcriptional activation in IFN-gamma inducible IRF-1 and Fc gamma RI genes in U937 cells. Together, our data indicate that IL-6 secretion and increased expression of the IFN-gamma R gene correlate with U937 cell growth arrest induced by IFN-gamma and PRL, probably through a signaling mechanism which does not involve the Stat 1/IRF-1 pathway.

L4 ANSWER 38 OF 79 MEDLINE

DUPLICATE 24

ACCESSION NUMBER: 96145220 MEDLINE

DOCUMENT NUMBER: 96145220 PubMed ID: 8558915

TITLE: Interleukin 4 and interferon gamma costimulate the expansion of early human

myeloid

colony-forming cells. Proposal of a model for the

regulation of myelopoiesis by interleukin 4 and

interferon gamma and its integration with the regulation of the immune response.

AUTHOR: Snoeck H W; Lenjou M; Nys G;

Lardon F; Peetermans M E; Van

Bockstaele D R; Moulijn A; Haenen L;

Berneman Z N

CORPORATE SOURCE: Laboratory of Experimental Hematology, University of

Antwerp (UIA), Belgium.

SOURCE: LEUKEMIA, (1996 Jan) 10 (1) 117-22.

Journal code: 8704895. ISSN: 0887-6924.

PUB. COUNTRY: ENGLAND: United Kingdom

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199602

ENTRY DATE: Entered STN: 19960312

Last Updated on STN: 19960312

Entered Medline: 19960226

AB We have previously shown that interleukin 4 (IL-4) and interferon

gamma (INF-gamma) reciprocally regulate the production of

granulocytes and monocytes from mature monopotential hematopoietic

progenitor cells, while at the level of the very primitive stem cells

IFN-gamma is a selective inhibitor of proliferation and differentiation,

and IL-4 has weak stimulatory effects. We

investigated the effects of IL-4

and IFN-gamma on the expansion in suspension culture of myeloid

colony-forming cells (CFCs) induced by either IL-3 or IL-1+IL-3, using on

the one hand more differentiated CD34+HLA-DR strongly

positive (HLA-DR++) and on the other hand more primitive Cd34+HLA-DR weakly positive (HLA-

DR+/-) human bone marrow cells. It is shown that both IL-4 and

IFN-gamma stimulate the IL-3- and IL-3+IL-1-induced expansion of

the number of CFCs in the HLA-DR+/- population. In the

presence, but not in the absence of IL-1, additive effects of IL-4 and

IFN-gamma were seen. We could not demonstrate any IL-3-like effect by IL-4

on early human hematopoietic progenitors. No expansion of CFC number was

seen in the HLA-DR++ population. Based on these data

and on data which we have published previously, a model for the regulation

of myelopoiesis by IL-4 and IFN-gamma is proposed. In this model, IL-4 and

IFN-gamma, which are both immune recognition induced inflammatory

cytokines, both stimulate the expansion and recruitment of early

myeloid progenitors, whereas at the level of their terminal

differentiation, the balance between both cytokines determines whether

preferentially monocytes/macrophages (IFN-gamma) or granulocytes (IL-4)

are being produced. At the level of the most primitive cells, the

inhibitory action of IFN-gamma might prevent differentiative exhaustion of

the stem cell compartment in situations of hematopoietic stress.

L4 ANSWER 39 OF 79 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1996:332173 CAPLUS

DOCUMENT NUMBER: 125:7867

TITLE: IFN-gamma-stimulated

enhancement of MHC class II

antigen expression by the human mast cell line HMC-1

AUTHOR(S): Love, Kelley S.; Lakshmanan, Romola R.; Butterfield,

Joseph H.; Fox, Charity C.

CORPORATE SOURCE: Dep. of Medical Microbiology and Immunology and

Internal Medicine, Ohio State Univ.

College of

Medicine, Columbus, OH, 43210, USA

SOURCE: Cellular Immunology (1996), 170(1), 85-90

CODEN: CLIMB8; ISSN: 0008-8749

PUBLISHER: Academic

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The expression of MHC class II mols. by human mast cells has been reported

in immunohistochem. surveys of inflammatory conditions, such as in

tuberculin hypersensitivity. While these data suggest that human mast

cells may act as antigen-presenting cells under inflammatory conditions,

the induction of class II antigens on human mast cells has not been examd.

In this study, we detd. the effects of the inflammatory cytokines

IFN-gamma. and IL-4 on the expression of class II antigens HLA-DR, -DP,

and -DQ by the human mast cell line HMC-1. HMC-1 cells were incubated

with or without 1000 U/mL recombinant human IFN-gamma. Z(rhIFN-gamma.)

and IL-4 (rhIL-4) for 72 h and analyzed for expression of MHC class II

antigens by direct immunofluorescence and flow cytometry. HMC-1 cells

expressed significant levels of HLA-DR and moderate levels of HLA-DP and

-DQ at baseline and when cultured without exogenous cytokines.

Stimulation by rhIFN-gamma. for 72 h significantly increased the levels

of HLA-DR and -DP expression but did not affect levels of HLA-DQ.

Stimulation by rhIL-4 for 72 h had minimal effect on expression of class

II mols., but induced a significant difference in levels of ICAM-1 (CD54)

expression, indicating that this cytokine is involved instead in the

control of certain accessory mols. Our data showing constitutive

expression of MHC class II mols. on HMC-1 cells and upregulation of that

expression by rhIFN-gamma. suggest that human mast cells function as

antigen-presenting cells at sites where inflammatory cytokines are

present.

L4 ANSWER 40 OF 79 MEDLINE

DUPLICATE 25

ACCESSION NUMBER: 96404648 MEDLINE

DOCUMENT NUMBER: 96404648 PubMed ID: 8808789

TITLE: IL-10 production by adult human derived microglial cells.

AUTHOR: Williams K; Dooley N; Ulvestad E; Becher B; Antel J P

CORPORATE SOURCE: Department of Pathology, Dartmouth Medical School,

Dartmouth-Hitchcock Medical Center, Lebanon, NH 03756, USA.

CONTRACT NUMBER: T32 AI 07363 (NIAID)

SOURCE: NEUROCHEMISTRY

INTERNATIONAL, (1996 Jul) 29 (1) 55-64.

Journal code: 8006959. ISSN: 0197-0186.

PUB. COUNTRY: ENGLAND: United Kingdom

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199612

ENTRY DATE: Entered STN: 19970128

Last Updated on STN: 19970128

Entered Medline: 19961204

AB Microglia, a population of central nervous system (CNS) macrophages, have

been demonstrated to support immune accessory and effector functions in

the CNS. Numerous studies support the role of microglia in CNS development

and pathology, where activation of microglia is consistently noted. The

current study investigated microglial immune functions under basal and

activation conditions and assessed the ability of interleukin-10 (IL-10),

added exogenously or produced by microglia, to down-regulate microglial

functions. This report demonstrates that microglia from the adult human brain produce IL-10 following interferon-gamma /lipopolysaccharide activation. Functionally, recombinant human IL-10 down-regulated basal HLA-DR expression by microglia and inhibited, in a dose-dependent response, the ability of microglia to stimulate CD4+ T-cells in antigen presentation assays. These data, together with recent observations of the inhibition of experimental allergic encephalomyelitis (EAE) following IL-10 administration and reduced CNS infection by *Listeria monocytogenes* after anti-IL-10 treatment, suggest that IL-10 production by microglia may have important immune-regulatory functions in CNS disease and disease models.

L4 ANSWER 41 OF 79 CANCERLIT
 ACCESSION NUMBER: 96602227 CANCERLIT
 DOCUMENT NUMBER: 96602227
 TITLE: Gene therapy of human melanoma by particle bombardment (Meeting abstract).
 AUTHOR: Albertini M R; Sheehy M J; Schell K; Emler C; Tans K; King D
 CORPORATE SOURCE: University of Wisconsin Comprehensive Cancer Center, Madison, WI 53792.
 SOURCE: Proc Annu Meet Am Assoc Cancer Res, (1995) 36 A2934.
 ISSN: 0197-016X.
 DOCUMENT TYPE: (MEETING ABSTRACTS)
 LANGUAGE: English
 FILE SEGMENT: Institute for Cell and Developmental Biology
 ENTRY MONTH: 199604
 ENTRY DATE: Entered STN: 19970509
 Last Updated on STN: 19970509

AB While progress has been made understanding the essential components required for effective T-cell recognition of human melanoma, this disease remains incurable once metastatic. This project utilizes particle-mediated gene transfer (PMGT) to deliver distinct genes to melanoma cells to stimulate anti-melanoma T-cell immunity. The necessary components for effective T-cell recognition include (1) a peptide antigen preferentially expressed in melanoma, (2) appropriate major histocompatibility (MHC) expression for presentation of the peptide and (3) co-stimulatory molecule expression. Established and early-passage human melanoma cell lines were bombarded with gold beads coated with human interferon-gamma (IFN- γ) cDNA. These transfected melanoma cell lines produced IFN- γ (28.8 pg/ml to 167.9 pg/ml) when evaluated 24, 48, and 72 hr following PMGT. The biologic effect of this

IFN- γ transgene included an upregulation of MHC class I expression and dramatic upregulation of MHC class II expression for HLA-DP and HLA-DR but not for HLA-DQ. These melanoma cell lines had no detectable surface expression of the B7-1 co-stimulatory molecule when evaluated by flow cytometry with the BB1 monoclonal antibody. Following PMGT with the human B7-1 cDNA, approximately 6% of the M-21 melanoma cells had detectable surface expression for B7-1. Ongoing experiments are aimed at enhancing the gene transfer efficiency as well as determining the in vitro immunogenicity of these IFN- γ and B7-1 transfected cells. The molecular modification of human melanoma cells can be successfully achieved by PMGT with the cDNAs for IFN- γ and for the B7-1 co-stimulatory molecule and presents a promising strategy to stimulate antimelanoma T-cell immunity.

L4 ANSWER 42 OF 79 MEDLINE
 DUPLICATE 26
 ACCESSION NUMBER: 96418518 MEDLINE
 DOCUMENT NUMBER: 96418518 PubMed ID: 8821303
 TITLE: Upregulation of IgE synthesis by staphylococcal toxic shock syndrome toxin-1 in peripheral blood mononuclear cells from patients with atopic dermatitis.
 AUTHOR: Hofer M F; Lester M R; Schlievert P M; Leung D Y
 CORPORATE SOURCE: Department of Paediatrics, National Jewish Center for Immunology and Respiratory Medicine, Denver, CO 80206, USA.
 CONTRACT NUMBER: AR-41256 (NIAMS) HL-37260 (NHLBI) RR-00051 (NCRR)
 +
 SOURCE: CLINICAL AND EXPERIMENTAL ALLERGY, (1995 Dec) 25 (12) 1218-27.
 Journal code: 8906443. ISSN: 0954-7894.

PUB. COUNTRY: ENGLAND: United Kingdom
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 199611
 ENTRY DATE: Entered STN: 19961219
 Last Updated on STN: 19961219
 Entered Medline: 19961105
 AB BACKGROUND: Atopic dermatitis (AD) is a chronic skin disease associated with increased IgE synthesis and colonization with *Staphylococcus aureus* secreting exotoxins, such as Toxic Shock Syndrome Toxin-1 (TSST-1).
 OBJECTIVES: In this study, we were interested in determining the in vitro effects of TSST-1 on IgE synthesis in peripheral blood mononuclear cells

from patients with AD. METHODS: We stimulated peripheral blood mononuclear cells (PBMC) from AD patients with a wide range of TSST-1 concentrations and measured IgE synthesis by enzyme-linked immunosorbent assay (ELISA) after 14 days. RESULTS: We show herein that TSST-1 produced antagonistic effects on IgE synthesis by PBMC from AD patients, depending on the concentration used: IgE synthesis was inhibited at 1000 pg/mL ($P < 0.05$) and enhanced at 0.01 pg/mL ($P < 0.01$) of toxin. TSST-1 was found to induce the production of much higher amounts of interferon-gamma (IFN gamma) at 1000 pg/mL than at 0.01 pg/mL of toxin ($P = 0.0001$). More importantly, immunoglobulin E (IgE) synthesis was enhanced by TSST-1 at 1 pg/mL in the presence of antibodies blocking IFN gamma activity. The other immunoglobulin (Ig) isotypes were also increased after TSST-1 stimulation suggesting that the enhanced IgE synthesis was secondary to a polyclonal B cell activation rather than an isotype switch. TSST-1-stimulated IgE synthesis was T cell-dependent because purified tonsil B cells were only able to synthesize increased amounts of IgE when small numbers of T cells were added to the cultures. Anti-HLA-DR and anti-LFA-1 monoclonal antibodies (MoAb) inhibited TSST-1-enhanced IgE synthesis, suggesting that the bridging of the T cell receptor (TCR) and major histocompatibility complex (MHC) class II on B cells was necessary for activation of B cell differentiation. CONCLUSION: These data indicate that staphylococcal superantigens are able, at concentrations inducing low amounts of IFN gamma, to stimulate IgE synthesis by PBMC from AD patients, and suggest that staphylococcal toxins may contribute to elevated IgE synthesis in AD.

L4 ANSWER 43 OF 79 MEDLINE
DUPLICATE 27

ACCESSION NUMBER: 96093889 MEDLINE
DOCUMENT NUMBER: 96093889 PubMed ID:
7576910

TITLE: HIV type 1 grown on interferon gamma
-treated U937 cells shows selective
increase in
virion-associated intercellular adhesion
molecule 1 and
HLA-DR and enhanced infectivity for CD4-
negative cells.

AUTHOR: Castilletti C; Capobianchi M R; Fais
S; Abbate I;
Ficociello B; Ameglio F; Cordiali Fei P;
Santini S M;

Dianzani F
CORPORATE SOURCE: Institute of Virology,
University La Sapienza, Rome.

SOURCE: AIDS RESEARCH AND HUMAN
RETROVIRUSES, (1995 May) 11 (5)
547-53.

Journal code: 8709376. ISSN: 0889-2229.

PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL
ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 199512
ENTRY DATE: Entered STN: 19960124
Last Updated on STN: 19970203
Entered Medline: 19951219

AB Cellular adhesion molecules, such as ICAM-1, -2, and -3; LFA-1; and HLA class I and II are incorporated into HIV-1 virions during budding from infected cells. These virion-associated molecules can be involved in the adsorption to susceptible cells displaying the corresponding counterligands. A number of cytokines have been shown to upregulate the cellular expression of adhesion molecules, such as ICAM-1 and HLA-DR. In this study we investigated the effects of IFN-gamma on the incorporation of ICAM-1, LFA-1, and HLA-DR into mature HIV-1 progeny from chronically infected cells. The ability of such virus progeny to infect either CD4-positive or -negative cells was also investigated. The results indicate that IFN-gamma stimulates the expression of ICAM-1 and of HLA-DR on HIV-1-infected cells, whereas LFA-1 expression is unaffected. The same modifications were also observed on virus progeny, because specific MAbs to ICAM-1 and HLA-DR captured infectious HIV-1 from IFN-treated cells with higher efficiency as compared to virus from control cells, whereas virus binding to anti LFA-1 MAb was unchanged. Moreover, the HIV-1 progeny released from IFN-treated cells showed an increased ability to bind to and to infect CD4-negative cells, whereas the infectivity was basically unchanged for CD4-positive cells. Our results suggest that cytokines, as well as other soluble factors, may expand the host cell range of HIV-1, possibly through modifications of the cell-derived surface molecules on the virions. (ABSTRACT TRUNCATED AT 250 WORDS)

L4 ANSWER 44 OF 79 MEDLINE
DUPLICATE 28

ACCESSION NUMBER: 95268072 MEDLINE
DOCUMENT NUMBER: 95268072 PubMed ID:
7749123

TITLE: Immune responses by cord blood cells.
AUTHOR: Roncarolo M G; Bigler M; Ciuti E;
Martino S; Tovo P A
CORPORATE SOURCE: DNAX Research Institute,
Human Immunology Department, Palo

Alto, CA 94304-1104, USA.
SOURCE: BLOOD CELLS, (1994) 20 (2-3) 573-85; discussion 585-6.

Journal code: 7513567. ISSN: 0340-4684.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199506
ENTRY DATE: Entered STN: 19950629

Last Updated on STN: 19950629
Entered Medline: 19950620

AB In the present study, the biological properties of cord blood cells were investigated. Cord blood mononuclear cells and T cells responded normally to activation by alloantigens in primary mixed leukocyte reactions (MLRs), indicating that cord blood T cells can be normally activated via their TcR and have normal proliferative capacities. In addition, they expressed normal levels of accessory molecules such as CD28 and LFA-1, which contribute to amplify their responses. In contrast, cord blood mononuclear cells, but not cord blood monocytes, had a reduced capacity to stimulate allogeneic cells in primary MLRs. In addition, cord blood monocytes express lower levels of HLA-DR and ICAM-1 compared to adult peripheral blood monocytes. Cord blood mononuclear cells were also impaired in their capacity to generate allogeneic cytotoxic activity in primary mixed leukocyte cultures (MLCs). In contrast, cord blood B cells were similar to adult B cells in their capacity to switch to immunoglobulin E producing cells when incubated with interleukin-4 (IL-4) and anti-CD40 monoclonal antibody. We also demonstrated that IL-2, IL-6, and tumor necrosis factor-alpha (TNF-alpha) production by activated cord blood mononuclear cells was comparable to that observed with peripheral blood mononuclear cells isolated from normal adult donors. In contrast, interferon-gamma (IFN-gamma) was significantly decreased, whereas IL-4 and IL-5 were absent. Granulocyte-macrophage colony-stimulating factor (GM-CSF) levels were in general higher in the supernatants of cord blood cells. Thus, cord blood immune responses differ from those of peripheral blood at several levels. Whether these differences account for a reduced capacity of transplanted cord blood cells to modulate graft vs. host disease remains to be determined.

L4 ANSWER 45 OF 79 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1994:104975 CAPLUS
DOCUMENT NUMBER: 120:104975

TITLE: Increased proliferation, cytotoxicity, and gene

expression after stimulation of human peripheral blood T lymphocytes through a surface ganglioside (GD3)
AUTHOR(S): Norihisa, Yoko; McVicar, Daniel W.; Ghosh, Paritosh; Houghton, Alan N.; Longo, Dan L.; Creekmore, Stephen P.; Blake, Trevor; Ortaldo, John R.; Young, Howard A.

CORPORATE SOURCE: Frederick Cancer Res. Dev. Cent., Natl. Cancer Inst., Frederick, MD, 21702-1201, USA

SOURCE: Journal of Immunology (1994), 152(2), 485-95

CODEN: JOIMA3; ISSN: 0022-1767

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Previous studies have suggested that gangliosides have an important role in cell signaling and recognition. However, their specific function in these processes has not been clearly defined. A mAb, R24, that reacts specifically with a cell surface ganglioside (GD3) has been demonstrated to stimulate proliferation of T cells derived from human peripheral blood.

In this study, the authors have investigated the mechanisms by which the R24 mAb affects T cell functions. The authors have obsd. that the R24 mAb stimulates GD3+ T cell proliferation, cytotoxicity, and surface

marker expression of IL-2R .alpha.-chain, IL-2R .beta.-chain, HLA

-DR, CD11a, and CD11c. Addnl., IFN-.gamma. activity but not

IL-1, IL-2, or IL-4 activity was present in culture supernatants 72 h

after R24 stimulation. In some donors, increased IL-6 and TNF-.alpha.

activity also was detected after R24 treatment.

Furthermore, R24 treatment resulted in translocation of c-rel, but little or no NF.kappa.B

p50 or p65, from the cytoplasm to the nucleus and an increase of

NF.kappa.B binding complexes contg. c-rel and p50. This treatment also

caused increased tyrosine phosphorylation of specific protein substrates.

R24-stimulated increases in proliferation, cytotoxicity, and cell surface

protein expression could be blocked by cyclosporin and staurosporine,

indicating that cyclophilin/calcineurin and protein kinase C may be

involved in the R24 signaling pathway. Addnl., herbimycin A, a tyrosine

kinase inhibitor, blocked the R24-stimulated

increase in proliferation but

not cytotoxicity at concns. consistent with specificity for tyrosine

kinases. Thus, multiple biochem. pathways are involved in the activation

of human T cells by R24.

L4 ANSWER 46 OF 79 CAPLUS COPYRIGHT 2003
ACS

ACCESSION NUMBER: 1996:382310 CAPLUS

DOCUMENT NUMBER: 125:84534

TITLE: Regulatory mechanism of IFN-
.gamma.-induced expression

of HLA class II antigen

AUTHOR(S): Koide, Yukio; Ryu, Keiko; Nezu,
Nobukazu; Yoshida,
Takato

CORPORATE SOURCE: Dep. Microbiol.,
Hamamatsu Univ. Sch. Medicine,
Hamamatsue, Japan

SOURCE: MHC, Major Histocompatibility
Complex (1994), 1(1),
27-28

CODEN: MMHCFO

PUBLISHER: Nippon Soshiki Tekigosei Gakkai

DOCUMENT TYPE: Journal

LANGUAGE: Japanese

AB .gamma. Interferon increased the level of antigen
HLA-DR

mRNA, i.e. stimulates antigen HLA-DR
expression, in T98G cells. The stimulation is
inhibited by tyrosine

kinase inhibitor: genistein, herbimycin and
tyrphostin.

L4 ANSWER 47 OF 79 CAPLUS COPYRIGHT 2003
ACS

ACCESSION NUMBER: 1993:601498 CAPLUS

DOCUMENT NUMBER: 119:201498

TITLE: Enhanced expression of HLA
molecules and stimulation
of autologous human tumor infiltrating
lymphocytes

cells with
following transduction of melanoma

.gamma.-interferon genes
AUTHOR(S): Ogasawara, Masahiro;
Rosenberg, Steven A.

CORPORATE SOURCE: Surg. Branch, Natl.
Cancer Inst., Bethesda, MD, 20892,
USA

SOURCE: Cancer Research (1993), 53(15),
3561-8

CODEN: CNREA8; ISSN: 0008-5472

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Gene therapy for cancer is being tested in clin.
trials using

tumor-infiltrating lymphocytes (TIL) or tumor cells
modified by the
insertion of genes coding for interleukin 2 or tumor
necrosis factor

.alpha.. In the present study, the authors
investigated the feasibility
of transducing human tumor cells with genes coding
for .gamma.-interferon

(IFN.gamma.) or .alpha.-interferon (IFN.alpha.),
which are two other

cytokines that can enhance host antitumor immune
responses. Tumor cells

from 12 melanoma and 2 renal cell carcinoma
patients were transduced with

retroviral vectors contg. the gene for IFN.gamma..
Northern blot anal.

showed IFN.gamma. transcription only in the
IFN.gamma. gene-transduced

cells. In both IFN.gamma.-secreting and non-
secreting tumor lines, the

cell surface expression of HLA class I and class II
mols. increased

following transduction. However, the magnitude of
the increase in HLA

expression appeared to be greater in tumor lines
secreting IFN.gamma..

Two melanoma cell lines were successfully
transduced with an IFN.alpha.

retroviral vector. Melanoma cells transduced with
the IFN.alpha. gene

contained IFN.alpha. RNA transcripts and secreted
large amts. of

IFN.alpha.. In contrast to cells transduced with the
IFN.gamma. gene, the

expression of HLA class II mols. was not increased
in the IFN.alpha.

gene-transduced cells. Finally, the authors tested
the ability of

HLA.Dr+ melanoma cells, which had been
transduced with

the IFN.gamma. gene, to stimulate specific cytokine
release by

autologous CD4+ TIL. Specific secretion of cytokine
by TIL occurred when

the TIL and IFN.gamma. gene-transduced tumor
cells were cultured together

but not when TIL were cultured alone or with control
nontransduced tumor

cells. These results suggest that mols. newly
expressed on the transduced

cells promoted antigen presentation and T-cell
responses against the

transduced tumor cells. The insertion of the
IFN.gamma. gene into

melanoma cells may be useful either for active
immunization against

melanoma or for the generation of TIL to be used in
adoptive

immunotherapy.

L4 ANSWER 48 OF 79 BIOSIS COPYRIGHT 2003
BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 1993:225273 BIOSIS

DOCUMENT NUMBER: PREV199395116448

TITLE: Accessory cell function of human
eosinophils:

HLA-DR-dependent, MHC-restricted
antigen-presentation and

IL-1-alpha expression.

AUTHOR(S): Weller, Peter F. (1); Rand, Thomas
H.; Barrett, Tonya;

Elovic, Aram; Wong, David T. W.; Finberg,
Robert W.

CORPORATE SOURCE: (1) Beth Israel Hosp., DA-
617, 330 Brookline Ave., Boston,
MA 02215

SOURCE: Journal of Immunology, (1993) Vol.
150, No. 6, pp.

2554-2562.

ISSN: 0022-1767.

DOCUMENT TYPE: Article

LANGUAGE: English

AB Although peripheral blood eosinophils express little
of the class II MHC

protein, HLA-DR, eosinophils could be induced to
express HLA-DR by exposures to cytokines,
including

granulocyte-macrophage-CSF, IL-4, and IFN-gamma, with granulocyte-macrophage-CSF eliciting the greatest level of HLA-DR expression as assessed by flow cytometry. The capacity of HLA-DR+ eosinophils to function as APC was evaluated with blood eosinophils isolated free of mononuclear cells, cultured with granulocyte-macrophage-CSF to induce HLA-DR expression and then exposed to the Ag tetanus toxoid. HLA-DR+ eosinophils fixed with paraformaldehyde after Ag exposure stimulated T cell proliferation, whereas HLA-DR+ eosinophils fixed with paraformaldehyde before Ag exposure failed to stimulate lymphocyte proliferation. The lymphocyte proliferative responses elicited by Ag-pulsed HLA-DR+ eosinophils were inhibited by anti-HLA-DR mAb and were restricted to HLA-DR compatible lymphocytes. Moreover, eosinophils from a hypereosinophilic donor, both before and more prominently after stimulation with PMA, contained transcripts for IL-1-alpha mRNA detectable by Northern blot hybridization and in situ hybridization and expressed IL-1-alpha protein detectable by immunohistochemistry. These findings indicate that human eosinophils can process Ag, express the costimulatory cytokine IL-1-alpha, and after cytokine-elicited induction of HLA-DR expression can function as HLA-DR-dependent, MHC-restricted APC in stimulating T lymphocyte responses.

L4 ANSWER 49 OF 79 MEDLINE
DUPLICATE 29

ACCESSION NUMBER: 93314692 MEDLINE
DOCUMENT NUMBER: 93314692 PubMed ID:
8100773

TITLE: Activation with superantigens induces
programmed death in
antigen-primed CD4+ class II+ major
histocompatibility
complex T lymphocytes via a
CD11a/CD18-dependent mechanism.

AUTHOR: Damle N K; Leytze G; Klussman K;
Ledbetter J A
CORPORATE SOURCE: Bristol-Myers Squibb
Pharmaceutical Research Institute,
Seattle.

SOURCE: EUROPEAN JOURNAL OF
IMMUNOLOGY, (1993 Jul) 23 (7) 1513-22.
Journal code: 1273201. ISSN: 0014-2980.

PUB. COUNTRY: GERMANY: Germany, Federal
Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL
ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199308

ENTRY DATE: Entered STN: 19930820

Last Updated on STN: 19950206

Entered Medline: 19930809

AB Staphylococcal enterotoxin superantigens (SAG) bind class II major histocompatibility complex (MHC) molecules on antigen-presenting cells (APC) and upon cell-to-cell contact stimulate proliferation of T cells expressing appropriate V beta gene products. In addition, SAG can also deliver negative signals to Ag-specific T cells resulting in a state of unresponsiveness or a loss of viability. The present study examines the functional consequences of a direct interaction of SAG with alloAg-specific class II MHC+ CD4+ T cell lines (TCL). Our results demonstrate that SAG induce programmed death (apoptosis) in a majority of Ag-specific CD4+ T cells accompanied by genomic DNA fragmentation. SAG binding to Ag-specific TCL resulted in a rapid mobilization of intracellular free calcium ([Ca2+]i) and transcription of a number of cytokine genes including interleukin-2(IL-2), IL-4, interferon-gamma (IFN-gamma), granulocyte-macrophage colony-stimulating factor (GM-CSF), and granzyme B indicating the activation of primed T cells. Both SAG-induced cytokine gene expression as well as subsequent death were significantly inhibited by a tyrosine kinase inhibitor herbimycin A and also by cyclosporin A. SAG-induced death of primed T cells was also inhibited by monoclonal antibodies (mAb) directed at the CD11a/CD18 molecule but not those reactive with other T cell surface molecules such as CD2, CD7, CD28, CD29 or CD49d. None of these mAb, including anti-CD11a/CD18, had any effect on SAG-induced expression of IL-2 and IL-4 genes or SAG-induced [Ca2+]i response. Addition of cytokines such as IL-1 alpha, IL-2, IL-4, IL-6, GM-CSF, IFN-gamma, tumor necrosis factor (TNF-alpha, or TNF-beta), or neutralizing Ab to these cytokines had no effect on SAG-induced death of Ag-specific TCL. The T cells which survived the death-inducing effects of SAG showed down-regulation of the CD3/T cell receptor and up-regulation of CD2 and HLA-DR expression, and upon re-exposure to the same SAG upregulated expression of mRNA for IL-2 and IFN-gamma. Presentation of SAG by B7+ ICAM-1+ LFA-3+ DR+ professional APC was also able to induce the death of Ag-specific TCL. Together these results suggest that the activation with SAG causes programmed death of Ag-specific TCL cells via a mechanism that requires late participation of the CD11a/CD18 molecule.

L4 ANSWER 50 OF 79 MEDLINE
 DUPLICATE 30
 ACCESSION NUMBER: 94061888 MEDLINE
 DOCUMENT NUMBER: 94061888 PubMed ID:
 8242663
 TITLE: Interleukin-4 plus tumor necrosis factor
 alpha augments the
 antigenicity of melanoma cells.
 AUTHOR: Hoon D S; Hayashi Y; Morisaki T;
 Foshag L J; Morton D L
 CORPORATE SOURCE: John Wayne Cancer
 Institute, Saint John's Hospital and
 Health Center, Santa Monica, CA 90404.
 CONTRACT NUMBER: CA 12582 (NCI)
 SOURCE: CANCER IMMUNOLOGY,
 IMMUNOTHERAPY, (1993 Nov) 37 (6) 378-84.
 Journal code: 8605732. ISSN: 0340-7004.
 PUB. COUNTRY: GERMANY: Germany, Federal
 Republic of
 DOCUMENT TYPE: Journal; Article; (JOURNAL
 ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 199401
 ENTRY DATE: Entered STN: 19940201
 Last Updated on STN: 19970203
 Entered Medline: 19940106
 AB Immune cytokines are important regulators of the
 immune response to
 neoplastic cells. We previously reported that
 interleukin 4 (IL-4) and
 either tumor necrosis factor alpha (TNF) or
 interferon
 gamma (IFN) synergistically inhibit melanoma cell
 growth and
 induce cell differentiation. In the present study we
 used various
 combinations of IL-4, IFN and TNF to enhance the
 antigenicity of melanoma
 cells. IL-4 plus TNF significantly increased the ability
 of melanoma cells
 to stimulate cytotoxic T cells (CTL) and act as
 targets of these
 CTL; IL-4 plus IFN was somewhat less effective,
 while TNF plus IFN was not
 as effective. IL-4 plus TNF also increased the
 expression of HLA class I
 and HLA-DR antigens on melanoma cells. The CTL
 lines
 examined in this study were CD3+CD4+ and
 oligoclonal. These preclinical
 results suggest that the immune response to
 melanoma whole-cell vaccines
 might be enhanced by pretreating vaccine cells with
 IL-4 plus TNF.

L4 ANSWER 51 OF 79 MEDLINE
 DUPLICATE 31
 ACCESSION NUMBER: 93325073 MEDLINE
 DOCUMENT NUMBER: 93325073 PubMed ID:
 7687392
 TITLE: Human CD4+ T cells proliferate to HLA-
 DR+ allogeneic
 vascular endothelium. Identification of
 accessory
 interactions.
 AUTHOR: Savage C O; Hughes C C; McIntyre
 B W; Picard J K; Pober J S
 CORPORATE SOURCE: Department of Vascular
 Biology and Section of

Transplantation Biology, Clinical Research
 Center, Harrow,
 U.K.
 CONTRACT NUMBER: HL 36028 (NHLBI)
 HL 43364 (NHLBI)
 SOURCE: TRANSPLANTATION, (1993 Jul) 56
 (1) 128-34.
 Journal code: 0132144. ISSN: 0041-1337.
 PUB. COUNTRY: United States
 DOCUMENT TYPE: Journal; Article; (JOURNAL
 ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 199308
 ENTRY DATE: Entered STN: 19930826
 Last Updated on STN: 19960129
 Entered Medline: 19930819
 AB Serially passaged human endothelial cell (EC)
 cultures will
 stimulate highly purified peripheral blood CD4+ T
 cells to
 proliferate if and only if the EC cultures are
 pretreated with IFN-gamma
 to induce de novo expression of MHC class II
 molecules, principally
 HLA-DR. HLA-DR-expressing EC alone
 appear sufficient to stimulate purified CD4+ T cell
 proliferation without the involvement of other
 leukocyte populations, as
 indicated by the following observations: (1) we find
 no contaminating
 leukocytes in our EC cultures by FACS analysis or
 fluorescence microscopy;
 specifically, there are no detectable CD45 or HLA-
 DR
 expressing cells; (2) neither the EC cultures nor the
 purified CD4+ T
 cells contain HLA-DR expressing cells detectable by
 polymerase chain reaction (PCR) of reverse-
 transcribed mRNA; (3) the
 stimulatory capacity of the EC cultures is maintained
 through serial
 subculture and through low-density replating,
 indicating that the
 stimulatory cell type must proliferate in culture as
 well as EC; and (4)
 in contrast to MLRs, the response to EC cultures is
 not inhibited by
 pretreatment of the stimulator cells and/or
 responding T cells with the
 monocyte toxin L-leucine-O-methyl ester. We have
 used mAb to investigate
 the role of various EC and T cell surface molecules
 in the T cell
 response. mAb to HLA-DR and CD4 inhibit
 proliferative
 responses of CD4+ T cells to EC cultures, as would
 be expected if T cells
 recognize and proliferate to IFN-gamma-induced
 allogeneic class II MHC
 molecules; whereas, also as expected, mAb to class
 I MHC molecules were
 without effect. Proliferation is also inhibited by mAbs
 to T cell CD2 and
 LFA-1 beta chain (CD18) and by mAbs to LFA-3
 (CD58) and CD44, which are
 expressed by T cells and EC. mAb to ICAM-1
 (CD54, a ligand for LFA-1)
 provides inconsistent inhibition, and mAb to ICAM-2,
 used with or without

anti-ICAM-1, is not inhibitory. Because both of these mAb block adhesion of LFA-1 expressing T cells to EC, our data suggest that additional ligands for LFA-1 must be important for allogeneic proliferation. mAb to VLA-4 alpha or beta chains (CD49d, CD29) enhance proliferation, presumably through direct costimulation of the T cells by these antibodies. However, a mAb to VCAM-1, an EC ligand for VLA-4, is partially inhibitory.(ABSTRACT TRUNCATED AT 400 WORDS)

L4 ANSWER 52 OF 79 MEDLINE
 DUPLICATE 32
 ACCESSION NUMBER: 93123336 MEDLINE
 DOCUMENT NUMBER: 93123336 PubMed ID: 8419398
 TITLE: Differential induction of stromelysin mRNA by bovine articular chondrocytes treated with interferon-gamma and interleukin-1 alpha.
 AUTHOR: Quintavalla J C; Berg R A; Beavis A J; Piccoli S P; Rediske J J; Kurkinen M; Patrick R A; Robertson F M
 CORPORATE SOURCE: Ciba-Geigy Pharmaceuticals, Summit, New Jersey 07901.
 SOURCE: JOURNAL OF CELLULAR PHYSIOLOGY, (1993 Jan) 154 (1) 113-21.
 Journal code: 0050222. ISSN: 0021-9541.
 PUB. COUNTRY: United States
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 199302
 ENTRY DATE: Entered STN: 19930226
 Last Updated on STN: 20000303
 Entered Medline: 19930205

AB Articular chondrocytes from rheumatoid joints have been shown to express class II major histocompatibility (MHC) antigens that were correlated with the presence of interferon-gamma (IFN-gamma) in the inflamed joint. Chondrocytes expressing MHC antigens function as antigen presenting cells and thus stimulate lymphocyte proliferation. These responses suggest a powerful role for the IFN-gamma stimulation of chondrocytes. The present studies were designed to examine the functional role of chondrocytes exposed to IFN-gamma during cartilage degradation that occurs in synovial disease. Destruction of cartilage in arthritis is partially attributable to metalloproteinases released by the chondrocytes in response to interleukin-1 (IL-1). Bovine articular chondrocytes treated with interleukin-1 alpha (IL-1 alpha) produced enhanced levels of stromelysin mRNA, however, Northern blots could not determine the percentage of cells responding. Exposure of bovine articular chondrocytes

to IFN-gamma induced the expression of bovine HLA-DR (boHLA-DR) antigen in 50% of the cells. Using a modified cell sorting technique, chondrocytes that expressed class II MHC antigens produced two fold greater stromelysin mRNA than chondrocytes that did not express this antigen. In contrast, collagen type II mRNA levels were similar in chondrocytes, regardless of the expression of class II MHC antigens. In situ hybridization studies showed that less than half of all cartilage chondrocytes were induced to synthesize stromelysin mRNA. These observations suggest that IFN-gamma stimulates specific subpopulations of chondrocytes to be functionally active in inflammation-induced metalloprotease secretion.

L4 ANSWER 53 OF 79 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
 ACCESSION NUMBER: 1993:118514 BIOSIS
 DOCUMENT NUMBER: PREV199395062614
 TITLE: IL-10 stimulates monocytes Fc-gamma-R surface expression and cytotoxic activity: Distinct regulation of antibody-dependent cellular cytotoxicity by IFN-gamma, IL-4, and IL-10.
 AUTHOR(S): Te Velde, Anje A.; De Waal Malefijt, Rene; Huijbens, Richard J. F.; De Vries, Jan E.; Figdor, Carl G. (1)
 CORPORATE SOURCE: (1) Div. Immunol., Neth. Cancer Inst., Plesmanlaan 121, 1066 CX Amsterdam Netherlands Antilles
 SOURCE: Journal of Immunology, (1992) Vol. 149, No. 12, pp. 4048-4052.
 ISSN: 0022-1767.
 DOCUMENT TYPE: Article
 LANGUAGE: English
 AB T cell-derived cytokines IFN-gamma and IL-4 have different regulatory effects on two functionally important molecules on human monocytes: MHC class II Ag and the Fc receptor for monomeric IgG, Fc-gamma-RI (CD64). MHC class II Ag, and Fc-gamma-RI are both upregulated in the presence of IFN-gamma. IL-4 induces MHC class II Ag expression but reduces Fc-gamma-RI expression. Recently, we showed that the cytokine IL-10 also affects MHC class II Ag expression. Here, we demonstrate that in contrast to the down-regulation of MHC class II Ag expression, IL-10 stimulates Fc-gamma-RI expression on human monocytes comparable to the levels of Fc-gamma-RI expression induced by IFN-gamma. The IL-10-induced Fc-gamma-RI expression is specific because anti-IL-10 antibodies completely reverse the IL-10-induced surface expression of

Fc-gamma-RI and correlate with an enhanced capacity to lyse anti-D-coated human rhesus-positive erythrocytes. IL-10 fails to induce the expression of Fc-gamma-RII (CD32) and Fc-gamma-RIII (CD16). Furthermore, we demonstrate that IL-10 is able to prevent down-regulation in surface membrane expression of all three Fc-gamma-R that can be found when monocytes are cultured in the presence of IL-4. In contrast to IFN-gamma, IL-10 does not restore the reduced antibody-dependent cellular cytotoxicity (ADCC) activity of IL-4-cultured monocytes. Together, these results show that, similar to IFN-gamma, IL-10 is capable of enhancing Fc-gamma-R expression and ADCC activity, and that IFN-gamma, IL-4, and IL-10 have different regulatory effects on both monocyte Ag-presenting capacity and ADCC activity.

L4 ANSWER 54 OF 79 MEDLINE
DUPLICATE 33

ACCESSION NUMBER: 92388674 MEDLINE

DOCUMENT NUMBER: 92388674 PubMed ID:
1517568

TITLE: IFN-gamma and 1,25(OH)2D3 induce
on THP-1 cells distinct
patterns of cell surface antigen expression,
cytokine
production, and responsiveness to contact
with activated T
cells.

AUTHOR: Vey E; Zhang J H; Dayer J M
CORPORATE SOURCE: Division of Immunology and
Allergy (Hans Wilsdorf
Laboratory), Hopital Cantonal Universitaire,
Geneve,
Switzerland.

SOURCE: JOURNAL OF IMMUNOLOGY,
(1992 Sep 15) 149 (6) 2040-6.
Journal code: 2985117R. ISSN: 0022-
1676.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL
ARTICLE)

LANGUAGE: English

FILE SEGMENT: Abridged Index Medicus Journals;
Priority Journals

ENTRY MONTH: 199210

ENTRY DATE: Entered STN: 19921023

Last Updated on STN: 19970203

Entered Medline: 19921007

AB Differentiation and maturation of monocytes are accompanied by the expression of specific surface glycoproteins, the secretion of cytokines, and the capacity to respond to ligands. These changes may be influenced by interactions with hormones, soluble lymphocytic products, or direct contact with lymphocytes. We have studied two distinct pathways in the differentiation of a human monocytic cell line, THP-1: one being induced by IFN-gamma and the other by 1 alpha,25-dihydroxyvitamin D3

(1,25(OH)2D3). In THP-1 cells, IFN-gamma induces cell surface expression of HLA-DR and CD54 and production of IL-1 beta, TNF-alpha, and IL-6. In contrast, 1,25(OH)2D3 increases cell surface expression of CD11b and CD14, but fails to stimulate cytokine production. Direct contact of THP-1 with stimulated fixed T cells markedly induces IL-1 beta, TNF-alpha, and IL-6 production by THP-1. Production is higher when THP-1 have been previously exposed to 1,25(OH)2D3 as compared to prior exposure to IFN-gamma. mAb raised against certain relevant cell surface glycoproteins on THP-1 were tested for their ability to block the response of THP-1 to T cells. Antibodies to CD11a, CD11b, and CD11c, alone or in combination, only partially blocked IL-1 beta production by THP-1, whereas antibodies to CD54 and CD14 did not. Thus other unknown structures on the THP-1 cells may be involved in the induction of THP-1 cytokine production by T cell contact.

L4 ANSWER 55 OF 79 CAPLUS COPYRIGHT 2003
ACS

ACCESSION NUMBER: 1993:20551 CAPLUS

DOCUMENT NUMBER: 118:20551

TITLE: The role of differential class II
antigen expression

in stimulation of allogeneic mixed
lymphocyte
reactions by human monocyte

hybridomas
AUTHOR(S): Shaked, Abraham; Hoyos,
Beatrice; Mayer, Lloyd
CORPORATE SOURCE: Dep. Surg., Mount Sinai
Med. Cent., New York, NY,
10029, USA

SOURCE: Transplantation (1992), 53(6),
1341-7

CODEN: TRPLAU; ISSN: 0041-1337

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The recognition of foreign class II antigens on accessory cells is the crux of an alloreactive immune response. This phenomenon is clearly demonstrated in the primary mixed lymphocyte reaction, which correlates with the type and d. of expressed gene products of the HLA-D region. A series of human monocyte hybridomas was generated by fusing monocytes with the hypoxanthine guanine phosphoribosyl transferase (HGPRT)-deficient, HLA-D antigen-neg. U937 histiocytic cell line. Clones bearing combination of HLA-DQ, -DP with or without HLA-DR were isolated, allowing for the functional assessment of these mols. In contrast to the U937 cells, the HLA-DR+DQ+DP+ clone 16.1 could stimulate a primary allogeneic MLR. Interestingly, the DR- but DP+DQ+ clones 13 and 15 also could stimulate alloreactive T cells, and the addn. of anti-DQ or

-DP but not -DR was assocd. with significant inhibition of the MLR response. Furthermore, .gamma.-IFN was found to have diverse effects on class II antigen expression in the U937 cells and the hybrids. .gamma.-IFN down-regulated the expression of HLA-DQ, -DP without altering -DR on clone 16.1, and this was assocd. with a redn. in its MLR stimulatory capacity. The MLR generated by this .gamma.-IFN-stimulated hybridoma (HLA-DR+DQ-DP-) was now unaffected by the addn. of anti-DQ or -DP mAbs. In contrast, up-regulation of DQ and DP antigens on the U937 cells by .gamma.-IFN now rendered these cells stimulatory in MLR. These data are consistent with the concept that DQ and DP are both important allostimulatory determinants. These results stress the potential importance of all D-region mols. in acute allograft rejection or successful engraftment.

L4 ANSWER 56 OF 79 MEDLINE
 DUPLICATE 34
 ACCESSION NUMBER: 92381704 MEDLINE
 DOCUMENT NUMBER: 92381704 PubMed ID: 1380987
 TITLE: Activation and differentiation of myelomonocytic cells in rheumatoid arthritis and healthy individuals--evidence for antagonistic in vitro regulation by interferon-gamma and tumor necrosis factor alpha, granulocyte monocyte colony stimulating factor and interleukin 1.
 AUTHOR: Seitz M; Zwicker M; Pichler W; Gerber N
 CORPORATE SOURCE: Division of Rheumatology, University Hospital, Inselspital, Bern, Switzerland.
 SOURCE: JOURNAL OF RHEUMATOLOGY, (1992 Jul) 19 (7) 1038-44.
 Journal code: 7501984. ISSN: 0315-162X.
 PUB. COUNTRY: Canada
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 199209
 ENTRY DATE: Entered STN: 19921018
 Last Updated on STN: 19960129
 Entered Medline: 19920925
 AB We analyzed expression of HLA-DR and CD14 molecules on myelomonocytic cells and its regulation by various inflammatory cytokines in 6 patients with rheumatoid arthritis (RA) and 4 healthy individuals who had undergone bone marrow aspiration. At start of the bone marrow culture there was a significantly higher number of HLA-DR and CD14 positive bone marrow mononuclear cells in patients with RA than in

normals. In addition, RA bone marrow mononuclear cells expressed an up to 10-fold higher mean density of both molecules than normal bone marrow mononuclear cells during the whole culture period of up to 14 days. The effect of the cytokines interferon-gamma (IFN-gamma), tumor necrosis factor alpha (TNF alpha), granulocyte monocyte colony stimulating factor (GM-CSF) and interleukin 1 (IL-1) on the expression of CD14 or HLA-DR was different: IFN-gamma strongly upregulated HLA-DR expression and down-regulated CD14 expression while TNF alpha, GM-CSF and IL-1 mainly stimulated CD14 expression on bone marrow mononuclear cells. Our data suggest that RA bone marrow mononuclear cells exhibit an activated phenotype and that TNF-alpha, GM-CSF and IL-1 mainly stimulate the differentiation of bone marrow macrophages whereas IFN-gamma activates them.

L4 ANSWER 57 OF 79 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
 ACCESSION NUMBER: 1993:74817 BIOSIS
 DOCUMENT NUMBER: PREV199395039317
 TITLE: Cellular responses to human chondrocytes: Absence of allogeneic responses in the presence of HLA-DR and ICAM-1.
 AUTHOR(S): Jobanputra, P.; Corrigan, V.; Kingsley, G.; Panayi, G. (1)
 CORPORATE SOURCE: (1) Rheumatology Unit, Div. Med., UMDS, Guy's Hosp., 4th Floor, Hunt's House, London SE1 9RT UK
 SOURCE: Clinical and Experimental Immunology, (1992) Vol. 90, No. 2, pp. 336-344.
 ISSN: 0009-9104.
 DOCUMENT TYPE: Article
 LANGUAGE: English
 AB To assess the accessory cell function of human articular chondrocytes, we assessed the ability of human chondrocytes to stimulate allogeneic peripheral blood mononuclear cells (PBMC) and to support phytohaemagglutinin (PHA)-induced proliferation of highly purified T cells. We also examined the surface expression of HLA-DR and ICAM-1 on the chondrocytes both unstimulated and stimulated with cytokines in vitro. Chondrocytes failed to stimulate allogeneic PBMC despite the constitutive expression of MHC class I molecules and the cytokine-induced expression of class II molecules but were able to support T cell proliferation to PHA, IFN-gamma and to a limited extent, IL-1-beta, induced class II expression on chondrocytes. ICAM-1 was present on 94-99% of freshly isolated cells; this declined with culture (17-59%; P lt 0.005)

but was readily induced by IFN-gamma, IL-1-beta, and tumour necrosis factor-alpha. Alloreactivity and, presumably, autoreactivity to chondrocytes requires factors in addition to the surface expression of DR and ICAM-1. However the presence of these molecules suggests a capacity for cell-cell interactions in inflammatory sites such as the cartilage pannus junction.

L4 ANSWER 58 OF 79 MEDLINE

DUPLICATE 35

ACCESSION NUMBER: 92010022 MEDLINE

DOCUMENT NUMBER: 92010022 PubMed ID: 1833315

TITLE: Activation of human natural killer cells by

lipopolysaccharide and generation of interleukin-1 alpha, beta, tumour necrosis factor and interleukin-6. Effect of IL-1 receptor antagonist.

AUTHOR: Conti P; Dempsey R A; Reale M; Barbacane R C; Panara M R; Bongrazio M; Mier J W

CORPORATE SOURCE: Immunology Division, School of Medicine, University of Chieti, Italy.

SOURCE: IMMUNOLOGY, (1991 Aug) 73 (4) 450-6.

Journal code: 0374672. ISSN: 0019-2805.

PUB. COUNTRY: ENGLAND: United Kingdom

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199110

ENTRY DATE: Entered STN: 19920124

Last Updated on STN: 19950206

Entered Medline: 19911030

AB The presence in the body of an antigen species or a bacterial lipopolysaccharide (LPS) has a pleiotropic effect on the immune system activating macrophages, lymphocytes and natural killer (NK) cells.

Recently it has been reported that human macrophages not only secrete

interleukin-1 (IL-1) but also its inhibitor, called IL-1 receptor

antagonist (IL-1ra), structurally similar to IL-1 beta, but with no

IL-1-like activity and which binds to the IL-1 receptor.

In this study we

show that LPS stimulates NK cell activity and IL-1ra potentiates

the stimulatory effect of human recombinant interleukin-2 (hrIL-2) on NK

cell activity. In addition, we found that hrIL-1ra inhibits DNA synthesis

in lymphocyte culture stimulated with

phytohaemagglutinin (PHA) (20

micrograms/ml), presumably via IL-1 inhibition. We also found that LPS is

a potent stimulator of monokines: IL-6, tumour necrosis factor-alpha

(TNF-alpha), and IL-1 beta, as determined by radioimmunoassay method, and

interferon-gamma (IFN-gamma), IL-2, TNF-alpha and IL-1

alpha, as determined by ELISA method, in

peripheral blood mononuclear

cells (PBMC). We used PBMC as effector cells since

LPS requires the

presence of accessory cells to activate lymphocytes

and bind to the

HLA-DR molecule on accessory cells. The effect of

LPS on

PBMC cytotoxicity has been compared with an

endotoxin-free extract of

Escherichia coli, OM-8990, which did not provoke

cytokine production nor

did it cause enhancement of NK cell activity. We

found that human

recombinant IL-1ra potentiates the stimulatory effect

of IL-2 on NK cell

activity, similar to hrIL-1 beta. The potentiation of IL-

2 in stimulating

NK cell activity by IL-1ra is not yet understood. Since

IL-1ra is a part

of the IL-1 family, it may work in a similar fashion to

IL-1, which also

potentiates IL-2 to enhance NK cell activity but has

been shown not to be

directly important in tumour cell killing. In addition,

hrIL-1ra can

amplify the effect of IL-2 on NK activity, possibly by

inhibiting the

cyclo-oxygenase products, which are

immunosuppressive and are generated in

antigen-stimulated PBMC cultures. The generation

of IFN-gamma by PBMC

after treatment with LPS strongly suggests that the

enhancement of NK cell

activity may be indirectly due to IFN production.

L4 ANSWER 59 OF 79 BIOSIS COPYRIGHT 2003

BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 1991:159569 BIOSIS

DOCUMENT NUMBER: BA91:85369

TITLE: ALLORECOGNITION OF HLA-DR AND

HLA-DQ TRANSFECTANTS BY HUMAN

CD45RA AND CD45R0 CD4 T CELLS

REPertoire ANALYSIS AND

ACTIVATION REQUIREMENTS.

AUTHOR(S): MERKENSCHLAGER M; IKEDA H;

WILKINSON D; BEVERLY P C L;

TROWSDALE J; FISHER A G; ALTMANN

D M

CORPORATE SOURCE: LABORATOIRE DE

GENETIQUE MOLECULAIRE DES EUKARYOCYTES

DU

CNRS, UNITE 184 DE BIOLOGIE

MOLECULAIRE ET DE GENIE

GENETIQUE DE L'INSERM, FACULTE

DE MEDECINE, 11 RUE HUMANN,

F-67085 STRASBOURG CEDEX,

FRANCE.

SOURCE: EUR J IMMUNOL, (1991) 21 (1), 79-88.

CODEN: EJIMAF. ISSN: 0014-2980.

FILE SEGMENT: BA; OLD

LANGUAGE: English

AB We have investigated the requirements for

allogeneic stimulation of human

CD4 T cells using HLA class II products expressed

on various cellular

backgrounds. Human (class II-negative RJ2.2.5 mutant) B cell lines transfected with HLA-DR or -DQ cDNA clones were efficient stimulators for highly purified CD4 T cells. HLA-DR-transfected mouse L cells or IFN- γ -induced human fibroblasts, although able to function as accessory cells for T cell responses to the mitogen PHA, failed to stimulate strong T cell alloresponses. On the basis of these observations, we have employed class II transfectants to address the following questions: (a) do CD45RA and CD45R0 subpopulations differ in their allogeneic activation requirements. (b) are these subpopulations skewed in their recognition of HLA-DQ vs. HLA-DR in a manner which might support the concept that CD45RA T cells are involved in HLA-DQ-restricted suppressor inducer functions and (c) by using transfectants expressing individual HLA-DR or -DQ heterodimers in combination with limiting dilution analysis, can one for the first time obtain estimates of precursor frequencies for allogeneic cells recognizing each of these class II isotypes? Our results show that CD45RA and CD45R0 T cells respond comparably to optimal numbers of stimulator cells. However, when CD45RA and CD45R0 T cell populations depleted of endogenous accessory cells were cultured with limiting numbers of stimulator cells, CD45R0 cells generally responded more strongly, consistent with the elevated levels of various adhesion molecules known to be expressed by this population. Further, we found a similar representation of responses to HLA-DR and -DQ antigens among populations expressing CD45RA and CD45R0 isoforms. Finally, the precursor frequencies of allogeneic CD4 T cells responding to particular HLA-DR alleles were higher than to -DQ, only by a factor of about 1.6, indicating that HLA-DQ recognition may occur more frequently than implied from previous antibody blocking studies.

L4 ANSWER 60 OF 79 MEDLINE

DUPLICATE 36

ACCESSION NUMBER: 90352394 MEDLINE

DOCUMENT NUMBER: 90352394 PubMed ID: 2117474

TITLE: Interferon gamma encapsulated into liposomes enhances the activity of monocytes and natural killer cells and has antiproliferative effects on tumor

cells in vitro.

AUTHOR: Rutenfranz I; Bauer A; Kirchner H
CORPORATE SOURCE: Institute of Immunology and Transfusion Medicine,

University of Lubeck, Federal Republic of

Germany.

SOURCE: BLUT, (1990 Jul) 61 (1) 30-7.

Journal code: 0173401. ISSN: 0006-5242.

PUB. COUNTRY: GERMANY, WEST: Germany, Federal Republic of

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199009

ENTRY DATE: Entered STN: 19901026

Last Updated on STN: 19970203

Entered Medline: 19900924

AB The effects of human interferon gamma (IFN gamma)

encapsulated into liposomes were investigated in vitro. Monocytes were

induced to release a cytotoxic factor with either IFN gamma encapsulated

into liposomes, free IFN gamma or

lipopolysaccharide (LPS). If IFN gamma

was applied in the liposomal form, less IFN activity was required to

stimulate monocytes. Most of the cytotoxic factor was secreted

during the first 4 h of stimulation. The cytotoxic factor in supernatants

from PMNLs was completely neutralized by a monospecific polyclonal

antiserum to tumor necrosis factor (TNF). Combining subthreshold doses of

IFN gamma liposomes or IFN gamma with

lipopolysaccharide synergistically

enhanced the release of TNF. In fluorescence

analysis, altered expression

of the class II HLA-DR antigen on LeuM3 positive

monocytes was induced with IFN gamma liposomes as well as with IFN gamma.

Not only monocytes but also natural killer (NK) cells were stimulated to

higher cytotoxicity by IFN gamma liposomes in a

dose-dependent manner. In

comparison with IFN gamma, the same amount of activity was necessary for

adequate stimulation of NK-cells against the K562 target cells.

Furthermore, the antiproliferative effects of IFN gamma liposomes and free

IFN gamma on several human tumor cell lines was compared. Among several

cell lines tested, U937 and A549 turned out to be

sensitive to IFN gamma,

and both cell lines reacted with 50% growth

inhibition at a lower amount

of gamma presented by liposomes than in the free form. These data show

production of IFN gamma liposomes which possess immunomodulatory and

antiproliferative activity in vitro. In several of the test systems

studied, liposome-encapsulated IFN gamma was more effective than free IFN

gamma.

L4 ANSWER 61 OF 79 MEDLINE

DUPLICATE 37

ACCESSION NUMBER: 89093934 MEDLINE

DOCUMENT NUMBER: 89093934 PubMed ID: 2492049

TITLE: Regulation of monocyte/macrophage C2 production and HLA-DR expression by IL-4 (BSF-1) and IFN-gamma.

AUTHOR: Littman B H; Dastvan F F; Carlson P L; Sanders K M

CORPORATE SOURCE: Rheumatology Section, McGuire V.A. Medical Center, Richmond, VA 23249.

SOURCE: JOURNAL OF IMMUNOLOGY, (1989 Jan 15) 142 (2) 520-5. Journal code: 2985117R. ISSN: 0022-1767.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals

ENTRY MONTH: 198902

ENTRY DATE: Entered STN: 19900308
Last Updated on STN: 19900308
Entered Medline: 19890214

AB IL-4 was originally described on the basis of its ability to co-stimulate the proliferation of resting B cells treated with anti-IgM. Recently, this cytokine has been shown to have other effects on mast cells, T cells, B cells, and macrophages. We studied the ability of IL-4 to regulate the production of C2 by human monocytes and monocytic cell lines and compared this with stimulation of HLA-DR expression, another recently described activity of IL-4. Responses to IL-4 were compared to IFN-gamma, a cytokine with both activities. IL-4 up-regulated C2 production by human monocytes and this effect was not inhibited by neutralizing anti-IFN-gamma antibody. IL-4 also stimulated C2 production by HL-60 cells that had been pre-treated with vitamin D3 to induce monocytic differentiation. IL-4 did not stimulate C2 production by U937 cells. IFN-gamma, in contrast to IL-4, stimulates C2 production by all three cell types. Although IL-4 increased C2 production by HL-60 cells we could not detect C2 mRNA by Northern blotting. However, co-stimulation of these cells with IL-4 and low concentrations of IFN-gamma resulted in an additive effect on C2 production and a greater increase in C2 mRNA than was seen with IFN-gamma alone. As reported by others, IL-4-stimulated HLA-DR expression by monocytes. In contrast to our findings regarding C2 production, stimulation of HLA-DR expression was inhibited by neutralizing anti-IFN-gamma mAb and IL-4 did not stimulate HLA-DR expression by U937 or HL-60 cells. IFN-gamma stimulated HLA-DR expression by all

three cell types. These results identify IL-4 as an additional cytokine able to directly stimulate C2 production by human monocytes and by a monocytic cell line whereas IL-4 stimulation of HLA-DR expression by monocytes appears to be IFN-gamma dependent.

L4 ANSWER 62 OF 79 MEDLINE
DUPLICATE 38
ACCESSION NUMBER: 89291526 MEDLINE
DOCUMENT NUMBER: 89291526 PubMed ID: 2525543

TITLE: Alloactivated HLA class II-positive T-cell lines induce IL-2 reactivity but lack accessory cell function in mixed leukocyte culture.

AUTHOR: Odum N; Dickmeiss E; Hofmann B; Jakobsen B K; Morling N; Platz P; Ryder L P; Geisler C; Svejgaard A

CORPORATE SOURCE: Department of Clinical Immunology, State University Hospital, Copenhagen, Denmark.

SOURCE: HUMAN IMMUNOLOGY, (1989 Jun) 25 (2) 135-48. Journal code: 8010936. ISSN: 0198-8859.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 198908

ENTRY DATE: Entered STN: 19900309
Last Updated on STN: 19900309
Entered Medline: 19890803

AB Recently, much interest has focused on the role of HLA class II antigens in T cell-T cell interactions. We have studied the stimulatory capability in the primary mixed leukocyte reaction and the primed lymphocyte reaction of 11 alloactivated, HLA-DR- or -DP-reactive CD4-positive T-cell lines (Ta). From 70 to 90% of the Ta were HLA class II-positive as judged by the reactions with HLA class II-reactive monoclonal antibodies, and the Ta carried the DR allospecificities of the original T-cell donor when typed in the microcytotoxic test using DR-specific alloantisera. Neither irradiated nor nonirradiated Ta stimulated primed lymphocytes directed against the relevant HLA class II antigens on the Ta. Interferon-gamma, recombinant interleukin 1, phorbol myristate acetate, calcium ionophore, and adherent cells had no effect on the stimulatory capability of Ta. The ability of irradiated Ta to stimulate in the primary mixed leukocyte reaction (median counts per minute (cpm) 5.5 x 10(3) was significantly lower than that of peripheral blood mononuclear cells (cpm: 44.0 x 10(3)). The stimulation by Ta was almost only seen when the Ta were specifically

directed against the class II antigens of the responder peripheral blood mononuclear cells (i.e., in combinations with "backstimulation") (median cpm: 21,000). In mixed leukocyte reaction combinations without backstimulation, significantly weaker reactions were seen (median cpm: 1,000). This observation may explain previous controversies concerning the stimulatory capacity of Ta. Recombinant interleukin 2 significantly enhanced the very low mixed leukocyte culture responses induced by class II-incompatible Ta in combinations without backstimulation but had no significant effect on cultures with Ta autologous to the responder peripheral blood mononuclear cells. Thus, allogeneic class II-positive Ta can induce interleukin 2 responsiveness but lack accessory cell function(s) necessary for the induction of interleukin 2 production in primed and unprimed T cells.

L4 ANSWER 63 OF 79 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
 ACCESSION NUMBER: 1990:28160 BIOSIS
 DOCUMENT NUMBER: BA89:15126
 TITLE: INDUCTION OF CLASS II HISTOCOMPATIBILITY ANTIGENS HLA-DR ON CELLS OF HUMAN COLONIC EPITHELIUM UNDER THE INFLUENCE OF GAMMA INTERFERON AND OF LAMINA PROPRIA LYMPHOCYTES.
 AUTHOR(S): RADWAN P; LOWES J; PRIDDLE J; JEWELL D
 CORPORATE SOURCE: KLINIKA GASTROENTEROL. AKAD. MED. LUBLINIE, UL. JACZEWSKIEGO 8, 20-950 LUBLIN.
 SOURCE: IMMUNOL POL, (1989) 14 (1), 37-44.
 CODEN: IMPODM. ISSN: 0324-8534.
 FILE SEGMENT: BA; OLD
 LANGUAGE: Polish
 AB Studies of expression of class II HLA antigens (HLA-DR) by maintained in vitro colonic epithelial cells of neoplastic origin were performed. The cells were exposed to various concentrations of gamma interferon (.gamma. IFN) and to supernatants from cultures of human lymphocytes isolated from lamina propria of normal colon and of colon from unspecific intestinal inflammations (NZJ). Reaction was evaluated qualitatively by immunohistochemical method with monoclonal antibody anti HLA-DR and also quantitatively by immunoenzymatic assay (micro-Elisa). It was found that both .gamma. IFN and lymphokines produced by lamina propria lymphocytes induce HLA -DR antigens on studied colonic epithelial cells. .gamma. IFN was found to stimulate HLA-DR expression in a dose independent way.

L4 ANSWER 64 OF 79 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
 ACCESSION NUMBER: 1988:256670 BIOSIS
 DOCUMENT NUMBER: BR34:127700
 TITLE: HUMAN IL-4-BSF-1 STIMULATES C2 PRODUCTION AND HLA-DR EXPRESSION BY HUMAN MONOCYTES-MACROPHAGES.
 AUTHOR(S): LITTMAN B H; CARLSON P L; SANDERS K M
 CORPORATE SOURCE: MCGUIRE V.A. MED. CENT. AND MED. COLL. VIRGINIA, VA. COMM. UNIV., RICHMOND, VA. 23249.
 SOURCE: 72ND ANNUAL MEETING OF THE FEDERATION OF AMERICAN SOCIETIES FOR EXPERIMENTAL BIOLOGY, LAS VEGAS, NEVADA, USA, MAY 1-5, 1988. FASEB (FED AM SOC EXP BIOL) J, (1988) 2 (4), ABSTRACT 3447.
 CODEN: FAJOEC. ISSN: 0892-6638.
 DOCUMENT TYPE: Conference
 FILE SEGMENT: BR; OLD
 LANGUAGE: English

L4 ANSWER 65 OF 79 MEDLINE
 DUPLICATE 39
 ACCESSION NUMBER: 88203652 MEDLINE
 DOCUMENT NUMBER: 88203652 PubMed ID: 2966398
 TITLE: Calcium influx and the Ca2+-calmodulin complex are involved in interferon-gamma-induced expression of HLA class II molecules on HL-60 cells.
 AUTHOR: Koide Y; Ina Y; Nezu N; Yoshida T O
 CORPORATE SOURCE: Department of Microbiology and Immunology, Hamamatsu University School of Medicine, Japan.
 SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1988 May) 85 (9) 3120-4.
 Journal code: 7505876. ISSN: 0027-8424.
 PUB. COUNTRY: United States
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 198806
 ENTRY DATE: Entered STN: 19900308
 Last Updated on STN: 19900308
 Entered Medline: 19880609
 AB Interferon gamma (IFN-gamma) induces HLA-DR and -DQ molecules and causes an accumulation of transcripts in HL-60 cells. Experiments were, therefore, designed to investigate the intracellular signaling molecules regulating the appearance of HLA class II molecules. The expression of HLA class II (DR and DQ) molecules induced by IFN-gamma was blocked by a calmodulin antagonist, W7, but not by a protein kinase C inhibitor, H7. Furthermore, a direct activator of protein kinase C, phorbol 12-myristate 13-acetate, was unable to induce HLA class II (DR) molecule expression. These results suggest that IFN-gamma induces

HLA class II molecules on HL-60 cells by way of a calcium-calmodulin pathway and not by way of a protein kinase C pathway. Calmodulin is activated by a transient rise in the cytosolic free calcium. In fact, IFN-gamma evoked a calcium influx into HL-60 cells, whereas depletion of Ca²⁺ from culture medium resulted in a failure of IFN-gamma to induce DR expression. Furthermore, the calcium ionophore A23187 by itself induced DR molecule expression. These results suggest that IFN-gamma stimulates calcium influx by a so-called receptor-mediated calcium channel and activates the calmodulin branch of the calcium messenger system, resulting in the induction of DR molecules on the surface of HL-60 cells.

L4 ANSWER 66 OF 79 MEDLINE
DUPLICATE 40

ACCESSION NUMBER: 88151077 MEDLINE
DOCUMENT NUMBER: 88151077 PubMed ID:
3125987

TITLE: Interferon gamma modulates the ability
of autologous non-T cells to stimulate T
cells to produce
and respond to interleukin 2.

AUTHOR: Kawano Y; Noma T; Itoh M; Yata J
CORPORATE SOURCE: Department of Pediatrics,
National Defense Medical College,
Saitama, Japan.

SOURCE: CELLULAR IMMUNOLOGY, (1988
Mar) 112 (1) 166-73.

Journal code: 1246405. ISSN: 0008-8749.

PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL
ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198804
ENTRY DATE: Entered STN: 19900308

Last Updated on STN: 19970203

Entered Medline: 19880412

AB The interactions of T-cell receptor with self-Ia antigen on non-T cells induced IL-2 production and IL-2 receptors on the cell surface and thus responsiveness to IL-2 of T cells in autologous mixed-lymphocyte reaction (AMLR). Four-day-cultured autologous non-T cells lost their ability to stimulate T cells to produce and respond to IL-2 with concurrent decrease of HLA-DR and HLA-DQ antigen expressed on the cell surface. Culturing of non-T cells with 500 U/ml of recombinant interferon gamma (IFN-gamma) maintained their stimulating ability which was otherwise lost. Treatment of non-T cells with monoclonal anti-HLA-DR or anti-HLA-DQ antibody before mixture with T cells abrogated their ability to induce IL-2 production and IL-2 responsiveness of T cells. The combined data suggested

that Ia antigen expressed on non-T cells is modulated by IFN-gamma, which increases the ability of non-T cells to stimulate autologous T cells to produce and respond to IL-2.

L4 ANSWER 67 OF 79 MEDLINE
DUPLICATE 41

ACCESSION NUMBER: 88210483 MEDLINE
DOCUMENT NUMBER: 88210483 PubMed ID:
3130193

TITLE: Interleukin-2-induced production of
interferon-
gamma by resting human T cells and large
granular
lymphocytes: requirement for accessory
cell factors,
including interleukin-1.

AUTHOR: Wilson A B; Harris J M; Coombs R R
CORPORATE SOURCE: Department of Pathology,
University of Cambridge, England.

SOURCE: CELLULAR IMMUNOLOGY, (1988
Apr 15) 113 (1) 130-42.

Journal code: 1246405. ISSN: 0008-8749.

PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL
ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198806
ENTRY DATE: Entered STN: 19900308

Last Updated on STN: 19970203

Entered Medline: 19880614

AB Between 5 and 20% of normal human lymphocytes were found to synthesize
interferon-gamma (IFN-gamma) in primary cultures
with

recombinant interleukin-2 (rIL-2). After 22 hr, IFN-
gamma-producing cells
included CD5+ T lymphocytes, CD16+ large
granular lymphocytes (LGL), and a
population of CD5-, CD16- blast cells. Only a small
proportion (0-7%) of
IFN-gamma-synthesizing cells expressed HLA-DR.
The

production of IFN-gamma by all rIL-2-responding
lymphocyte subsets was
shown to require the presence of DR+ accessory
cells, probably including
nonadherent, esterase-negative monocytes and/or
dendritic cells. Accessory
cell function in lymphocyte preparations depleted of
DR+ cells, or in
purified (greater than or equal to 95%) suspensions
of LGL, was fully
replaced either by addition of 2% autologous,
adherent monocytes or by
monocyte culture supernatant. The activity of
monocyte supernatant was
greatly reduced by treatment with antiserum specific
for human
interleukin-1 beta (IL-1 beta), although a
combination of rIL-1 beta and
rIL-2 failed to stimulate IFN-gamma production in
DR-

lymphocytes. These results indicate that rIL-2-
induced IFN-gamma synthesis
in both T cells and LGL requires the synergistic
activity of IL-1, and

possibly of one or more other monokines, as yet unidentified.

L4 ANSWER 68 OF 79 MEDLINE

DUPLICATE 42

ACCESSION NUMBER: 88269840 MEDLINE

DOCUMENT NUMBER: 88269840 PubMed ID: 2455573

TITLE: Enhancement of release from MHC class II antigen-positive monocytes of hematopoietic colony stimulating factors CSF-1 and G-CSF by recombinant human tumor necrosis factor-alpha: synergism with recombinant human interferon-gamma.

AUTHOR: Lu L; Walker D; Graham C D; Waheed A; Shadduck R K; Broxmeyer H E

CORPORATE SOURCE: Department of Medicine, Indiana University School of Medicine, Indianapolis 46223.

CONTRACT NUMBER: CA 15237 (NCI)

CA 36464 (NCI)

CA 36740 (NCI)

SOURCE: BLOOD, (1988 Jul) 72 (1) 34-41. Journal code: 7603509. ISSN: 0006-4971.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals

ENTRY MONTH: 198808

ENTRY DATE: Entered STN: 19900308

Last Updated on STN: 19970203

Entered Medline: 19880819

AB The influence of purified recombinant human tumor necrosis factor-alpha (rhuTNF-alpha) was assessed alone and in combination with purified recombinant human interferon gamma (rhuIFN-gamma) for its effects on enhancing release from human monocytes of activities that stimulate colony formation by granulocyte-macrophage (CFU-GM), erythroid (BFU-E), and multipotential (CFU-GEMM) progenitor cells. RhuTNF-alpha or rhuIFN-gamma enhanced release of colony stimulating factors (CSFs), which were determined by a combination of human and mouse colony assays, morphological assessment of colony types and neutralization studies with anti-human macrophage CSF (CSF-1) and anti-human granulocyte (G)-CSF to be CSF-1 and G-CSF. The activity in the uninduced and induced monocyte conditioned media (CM) for CFU-GM-type colonies and clusters was attributed to the presence of both CSF-1 and G-CSF, while the activity in the monocyte CM for BFU-E and CFU-GEMM colonies was attributed to the presence of G-CSF. Monocytes were separated by two-color fluorescence using a dye laser flow cytometry system with cells labeled with anti-leu

M3 conjugated with fluorescein isothiocyanate and anti-HLA-

DR conjugated with phycoerythrin. While

"constitutive" release of

CSFs from monocytes was apparent from both the leu M3+, HLA-

DR+ and the leu M3+, HLA-DR- (low density or negative DR) fractions, enhanced release of CSFs in response to

rhuTNF-alpha or rhuIFN-gamma was confined to the leu M3+, HLA-

DR+ population of cells. RhuTNF-alpha and rhuIFN-gamma synergized

to enhance release of CSFs such that low concentrations of each molecule,

which were inactive when used alone, were active when the two molecules

were used together. These studies suggest a role, at least in vitro, for

TNF-alpha and IFN-gamma in the release of CSFs from cells of the

mononuclear phagocytic lineage.

L4 ANSWER 69 OF 79 CANCERLIT

ACCESSION NUMBER: 89650502 CANCERLIT

DOCUMENT NUMBER: 89650502

TITLE: INTERFERON EFFECTS ON CELLULAR AND HUMORAL IMMUNITY.

AUTHOR: De Maeyer E; De Maeyer-Guignard J

CORPORATE SOURCE: Institut Curie-Biologie, Bat. 110, Campus d'Orsay, 91405

Orsay, France.

SOURCE: Non-serial, (1987) The Interferon

System. A Current Review

to 1987. Baron S et al, eds. The University of Texas

Medical Branch Series in Biomedical

Science, Austin, TX,

University of Texas Press, p. 327-35, 1987.

DOCUMENT TYPE: Book; (MONOGRAPH)

General Review; (REVIEW)

(REVIEW, TUTORIAL)

LANGUAGE: English

FILE SEGMENT: Institute for Cell and

Developmental Biology

ENTRY MONTH: 198904

ENTRY DATE: Entered STN: 19941107

Last Updated on STN: 19960517

AB Results of recent studies on effects of interferons

(IFNs) on cellular and

humoral immunity are reviewed under the following

headings: expression of

cell surface molecules--antigens and receptors

(antigens of the major

histocompatibility complex [MHC], effects on other cell surface

molecules), interaction with interleukin 2 (IL2),

macrophage activation,

and effects on B cells. It was previously shown that

recombinant human

IFN-gamma (rHuIFN-gamma) can increase the

synthesis and expression of the

Class II MHC antigens, HLA-DR, on human

monocytes;

recent evidence indicates that rHuIFN-gamma also induces the expression of

Class II antigens HLA-DR and HLA-DQ on tumor cells of

various origins, such as melanoma cells, glioma cells, and cells from several human carcinoma lines. Normal fibroblasts also can express Class II antigens when induced with IFN-gamma. In addition, IFN-gamma has been shown to modulate Class II HLA antigen expression on cultured thymic epithelial cells, and this finding raises the possibility that IFN-gamma participates in mechanisms that assure the permanent expression of these antigens on thymic epithelial cells in vivo. IFN-gamma is the prime inducer of expression of Class II antigens, while IFN-alpha and -beta play only secondary roles in this respect; however, expression of Class I antigens is usually readily induced by all three IFN species. Class I HLA cell lines having high or low responses to HuIFN-alpha have been isolated from the human thymus leukemia cell line Molt 4. A natural role for HuIFN-beta in the turning on of Class I HLA antigens during cell differentiation was strongly suggested by experiments, in which the appearance of Class I antigens during differentiation of cells of a lymphoma line to macrophages was inhibited by treatment with anti-IFN-beta serum. This observation points to IFNs as natural modulators during the normal differentiation process of cells derived from the hematopoietic system. Enhanced expression of histocompatibility antigens is but one manifestation of the ability of IFNs to stimulate the expression of genes coding for cell-surface molecules important for immune reactions; eg, the number of cellular receptors for tumor necrosis factor is significantly enhanced by treatment with IFN-gamma and, to a lesser extent, with IFN-alpha and -beta. Other cell surface receptor molecules influenced by IFN-gamma treatment are IL2 receptors on human peripheral blood monocytes, which are enhanced, and transferrin receptors on murine peritoneal macrophages, which are downregulated. Finally, interactions of IFNs with IL2, macrophage activation by IFNs, and effects of IFN-gamma on B cells are reviewed. (64 Refs)

L4 ANSWER 70 OF 79 MEDLINE
DUPLICATE 43

ACCESSION NUMBER: 88024285 MEDLINE
DOCUMENT NUMBER: 88024285 PubMed ID:
3117066

TITLE: Effects of gold sodium thiomalate on
interferon stimulation
of C2 synthesis and HLA-DR expression
by human monocytes.

AUTHOR: Sanders K M; Carlson P L; Littman B
H

CORPORATE SOURCE: Department of Medicine,
Medical College of Virginia,
Virginia Commonwealth University,
Richmond.

CONTRACT NUMBER: 5-732-CA 09210-08 (NCI)
SOURCE: ARTHRITIS AND RHEUMATISM,
(1987 Sep) 30 (9) 1032-9.

Journal code: 0370605. ISSN: 0004-3591.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL
ARTICLE)

LANGUAGE: English

FILE SEGMENT: Abridged Index Medicus Journals;
Priority Journals

ENTRY MONTH: 198711

ENTRY DATE: Entered STN: 19900305

Last Updated on STN: 19970203

Entered Medline: 19871104

AB Gamma-interferon (gamma-IFN) is a T cell-derived lymphokine that has potent macrophage-activating properties. It increases

Fc receptor density, increases the formation and release of reactive oxygen intermediates, increases the synthesis and release of complement cascade proteins, especially C2 and factor B, and increases class II (HLA-DR) antigen expression. These effects may play a

role in the potentiation of inflammation in rheumatoid arthritis. We examined the possibility that gold sodium thiomalate (GST), an effective

treatment for rheumatoid arthritis, would inhibit gamma-IFN-mediated stimulation of monocyte/macrophages. GST in

concentrations attainable in vivo was shown to inhibit both spontaneous and gamma-IFN-stimulated C2 production up to 50%. GST inhibition could be only partially overcome with

increasing concentrations of gamma-IFN. In addition, GST inhibited gamma-IFN-stimulated HLA-DR expression at the highest

concentrations tested (20-50 micrograms/ml). GST alone in low concentrations (0.1-5 micrograms/ml) was found to increase HLA-

DR antigen expression as quantitated by several methods, including

flow cytometry, cell surface enzyme-linked immunosorbent assay, and

Western blotting. This GST-stimulated increase in HLA-DR

antigen expression paralleled an increased ability of monocytes to present

antigen. The mechanism by which low concentrations of GST

stimulate HLA-DR antigen expression is unclear, but was shown by 35S-methionine cell labeling not to involve increased HLA-DR protein synthesis.

L4 ANSWER 71 OF 79 MEDLINE
DUPLICATE 44

ACCESSION NUMBER: 87252239 MEDLINE
DOCUMENT NUMBER: 87252239 PubMed ID:
3110281

TITLE: Differential presentation of HLA-DR, DQ, and DP restriction elements by interferon-gamma-treated dermal fibroblasts.

AUTHOR: Maurer D H; Hanke J H; Mickelson E; Rich R R; Pollack M S

CONTRACT NUMBER: AI15394 (NIAID)
AM33988 (NIADDK)
CA40552 (NCI)

SOURCE: JOURNAL OF IMMUNOLOGY,
(1987 Aug 1) 139 (3) 715-23.
Journal code: 2985117R. ISSN: 0022-1767.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals

ENTRY MONTH: 198708

ENTRY DATE: Entered STN: 19900305
Last Updated on STN: 19970203
Entered Medline: 19870826

AB IFN-gamma has been reported to induce expression of HLA class II (DR, DQ, DP) antigens on cultured human dermal fibroblasts (FB) by stimulating the de novo transcription of the alpha and beta chain genes of HLA-DR, -DQ, and -DP in these cells. We examined the relative nominal

and alloantigen-presentation capacity of each HLA class II gene product on FB by using CD4-positive, TNP-specific T cell clones restricted by

determinants on DR, DQ, or DP molecules, as well as allospecific, CD4-positive T cell clones recognizing DR-, DQ-, or DP-lymphocyte

activating determinants. After IFN-gamma exposure, FB strains used for antigen presentation displayed a high percentage of DR-positive cells and a much smaller percentage of DP-positive cells, but no detectable

DQ-positive cells by immunofluorescent techniques. FB stimulator cells

supported proliferative responses of two DR-allospecific T cell clones and one TNP-specific, DR-restricted clone, but not another TNP-specific,

DR-restricted clone. Despite only modest DP expression, FB stimulated both a TNP-specific, DP-restricted clone and a DP-allospecific T cell line.

However, IFN-gamma treated FB failed to stimulate a

TNP-specific, DQ-restricted clone and a DQ-allospecific clone. Our data

indicate that IFN-gamma differentially regulates expression of functional

class II lymphocyte activating determinants on FB antigen-presenting cells

and that FB may fail to support DQ-directed T cell responses due to

insufficient expression of DQ molecules on the FB cell surface. However,

the quantity of DR or DP expressed on FB did not directly correlate with

their ability to support T cell responses, indicating that additional factors, such as differences in T cell clone activation requirements, contribute to the capacity of FB to present class II allo- and antigen-restricting epitopes.

L4 ANSWER 72 OF 79 MEDLINE

DUPLICATE 45

ACCESSION NUMBER: 87084761 MEDLINE
DOCUMENT NUMBER: 87084761 PubMed ID: 3098840

TITLE: Dissection of defective antigen presentation by

interferon-gamma-treated fibroblasts.

AUTHOR: Geppert T D; Lipsky P E

CONTRACT NUMBER: AM-09989 (NIADDK)

SOURCE: JOURNAL OF IMMUNOLOGY,
(1987 Jan 15) 138 (2) 385-92.

Journal code: 2985117R. ISSN: 0022-

1767.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals

ENTRY MONTH: 198702

ENTRY DATE: Entered STN: 19900302
Last Updated on STN: 19970203

Entered Medline: 19870218

AB The capacity of interferon-gamma (IFN-gamma)-treated

HLA-DR expressing human dermal fibroblasts (FB) to

function as antigen-presenting cells (APC) was examined. FB were cultured

with 250 U/ml IFN-gamma for 4 days to induce HLA-DR

expression. Peripheral blood monocytes (M phi), FB, or IFN-gamma-treated

FB from the same donor were then cultured overnight with or without the

recall antigen streptokinase streptodornase (SKSD), and their capacity to

stimulate autologous T4 cell DNA synthesis was examined.

SKSD-bearing M phi stimulated T4 cell proliferation, whereas

antigen-bearing HLA-DR (+) FB did not. Even after fixation with paraformaldehyde to eliminate metabolic activity,

SKSD-bearing M phi, but not FB, were able to function as APC. However,

when HLA-DR (-) endothelial cell (EC) or autologous or

HLA-D-mismatched M phi were added to the cultures, antigen-pulsed

IFN-gamma-treated FB and M phi were comparably effective stimulators of

autologous T4 cell DNA synthesis. Antigen recognition by the T4 cell was

restricted by the class II major histocompatibility complex (MHC)-encoded

gene products expressed by the IFN-gamma-treated FB and was unrelated to

the class I or II MHC-encoded gene products expressed by the additional

cell type. EC-promoted T4 cell DNA synthesis induced by antigen-bearing IFN-gamma-treated FB was inhibited by 60.3, a monoclonal antibody directed at an epitope common to LFA-1, CR3, and the p150,95 molecule. Inhibition caused by 60.3 was completely reversed by the addition of IL 2 to the cultures. Antigen presentation by IFN-gamma-treated FB was also enhanced somewhat by IL 1, IL 2, or monoclonal antibody directed at Tp44 (9.3). However, each of these additions alone promoted T cell proliferation less effectively than EC and resulted in responses that were smaller than those triggered by antigen-bearing M phi. The data suggest that IFN-gamma-treated FB take up and process antigen effectively, but lack an accessory cell property necessary for antigen-induced T4 cell IL 2 production and proliferation.

L4 ANSWER 73 OF 79 MEDLINE
DUPLICATE 46

ACCESSION NUMBER: 87224172 MEDLINE
DOCUMENT NUMBER: 87224172 PubMed ID:
3108402

TITLE: Interferon-gamma regulates the T cell
response to precursor nevi and biologically
early melanoma.

AUTHOR: Guerry D 4th; Alexander M A; Elder
D E; Herlyn M F

CONTRACT NUMBER: CA 25874 (NCI)
CA 29200 (NCI)
CA25298 (NCI)

SOURCE: JOURNAL OF IMMUNOLOGY,
(1987 Jul 1) 139 (1) 305-12.

Journal code: 2985117R. ISSN: 0022-

1767.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL
ARTICLE)

LANGUAGE: English

FILE SEGMENT: Abridged Index Medicus Journals;
Priority Journals

ENTRY MONTH: 198707

ENTRY DATE: Entered STN: 19900305

Last Updated on STN: 19970203

Entered Medline: 19870723

AB To examine the potential regulatory role of
interferon-

gamma in the cellular immune response to
melanoma and its
precursor lesions, we have tested the capacity of
this lymphokine to
enhance HLA class II antigen-dependent T
lymphocyte blastogenesis, its in
vitro production by autologous T cells stimulated by
melanoma, and its
presence in melanocytic lesions in situ. Cell lines
derived from a
dysplastic nevus, a radial growth phase primary
tumor, a vertical growth
phase primary, and metastatic lesions were induced
by recombinant
interferon-gamma to express increased amounts of
HLA

class II antigens. Such cells were then examined in
radioimmunoassay for
expression of HLA-DR antigens and in co-culture for
their ability to stimulate proliferation of autologous T
cells.

Interferon-gamma treatment of melanocytic cells
increased their expression of HLA-DR antigens
threefold to sixfold. In parallel with these findings,
co-culture of T
cells with interferon-treated cells of a dysplastic
nevus and a radial
phase melanoma led to augmented T cell
incorporation of tritiated
thymidine, and this stimulation was inhibited with a
monoclonal antibody
to HLA-DR antigens. Despite augmented expression
of

HLA class II antigens (HLA-DR, -DQ, and -DP),
vertical
growth phase and metastatic melanoma cells failed
to stimulate
autologous T cells. When T cells were co-cultured
with stimulating
melanoma cells, culture supernatants contained
significantly increased
amounts of interferon-gamma (12 U/ml) in
comparison
with supernatants of T cells alone (4 U/ml). No
interferon was detectable
in cultures of melanoma cells alone. To link these in
vitro phenomena to
in situ events, we used murine monoclonal
antibodies to interferon
-gamma, the interleukin 2 receptor, and HLA-DR
antigens in an immunoperoxidase system to detect
interferon production and
lymphocyte activation in frozen sections of lesions
representative of
melanocytic tumor progression. In these studies,
precursor dysplastic nevi
and radial phase melanomas contained the highest
numbers of activated
lymphocytes and stained positively for interferon-
gamma

. These results suggest that interferon-gamma plays
a

central role in the regulation of the cellular immune
response to
melanoma. It is produced by T cells, likely activated
by tumor antigens
seen in the context of HLA class II antigens. In turn,
interferon
-gamma production enhances expression of HLA
class II antigens
by melanoma and precursor cells, and such
enhancement is associated with
additional T cell activation in a positive feed-back
loop.

L4 ANSWER 74 OF 79 EMBASE COPYRIGHT 2003
ELSEVIER SCI. B.V.

ACCESSION NUMBER: 87159300 EMBASE

DOCUMENT NUMBER: 1987159300

TITLE: Interferon-gamma. regulates the T cell
response to precursor nevi and biologically
early melanoma.

AUTHOR: Guerry IV D.; Alexander M.A.; Elder
D.E.; Herlyn M.F.

CORPORATE SOURCE: Pigmented Lesion Study
Group, The Hematology-Oncology

Section, Department of Medicine,
University of Pennsylvania
School of Medicine, Philadelphia, PA,
United States
SOURCE: Journal of Immunology, (1987) 139/1
(305-312).
CODEN: JOIMA3
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 037 Drug Literature Index
005 General Pathology and Pathological
Anatomy
026 Immunology, Serology and
Transplantation
016 Cancer
LANGUAGE: English
AB To examine the potential regulatory role of
interferon-
gamma. in the cellular immune response to
melanoma and its
precursor lesions, we have tested the capacity of
this lymphokine to
enhance HLA class II antigen-dependent T
lymphocyte blastogenesis, its in
vitro production by autologous T cells stimulated by
melanoma, and its
presence in melanocytic lesions in situ. Cell lines
derived from a
dysplastic nevus, a radial growth phase primary
tumor, a vertical growth
phase primary, and metastatic lesions were induced
by recombinant
interferon-gamma. to express increased amounts of
HLA
class II antigens. Such cells were then examined in
radioimmunoassay for
expression of HLA-DR antigens and in coculture for
their ability to stimulate proliferation of autologous T
cells.
Interferon-gamma. treatment of melanocytic cells
increased their expression of HLA-DR antigens
threefold to sixfold. In parallel with these findings,
co-culture of T
cells with interferon-treated cells of a dysplastic
nevus and a radial
phase melanoma led to augmented T cell
incorporation of tritiated
thymidine, and this stimulation was inhibited with a
monoclonal antibody
to HLA-DR antigens. Despite augmented expression
of
HLA class II antigens (HLA-DR, -DQ, and -DP),
vertical
growth phase and metastatic melanoma cells failed
to stimulate
autologous T cells. When T cells were co-cultured
with stimulating
melanoma cells, culture supernatants contained
significantly increased
amounts of interferon-gamma. (12 U/ml) in
comparison
with supernatants of T cells alone (4 U/ml). No
interferon was detectable
in cultures of melanoma cells alone. To link these in
vitro phenomena to
in situ events, we used murine monoclonal
antibodies to interferon
-gamma., the interleukin 2 receptor, and HLA-
DR antigens in an immunoperoxidase system to
detect interferon

production and lymphocyte activation in frozen
sections of lesions
representative of melanocytic tumor progression. In
these studies,
precursor dysplastic nevi and radial phase
melanomas contained the highest
numbers of activated lymphocytes and stained
positively for
interferon-gamma.. These results suggest that
interferon-gamma. plays a central role in the
regulation of the cellular immune response to
melanoma. It is produced by
T cells, likely activated by tumor antigens seen in the
context of HLA
class II antigens. In turn, interferon-gamma.
production enhances expression of HLA class II
antigens by melanoma and
precursor cells, and such enhancement is
associated with additional T cell
activation in a positive feed-back loop.

L4 ANSWER 75 OF 79 CAPLUS COPYRIGHT 2003
ACS

ACCESSION NUMBER: 1987:526636 CAPLUS

DOCUMENT NUMBER: 107:126636

TITLE: Augmentation by an organic
germanium compound Ge-132
of HLA-DR antigen- and IgG-Fc
receptor-expression on
human macrophages

AUTHOR(S): Hanaumi, Kiyoshi; Kumagai,
Katsuo

CORPORATE SOURCE: Sch. Dent., Tohoku
Univ., Sendai, Japan

SOURCE: Ensho (1987), 7(3), 253-8

CODEN: ENSHEE; ISSN: 0389-4290

DOCUMENT TYPE: Journal

LANGUAGE: Japanese

AB Ge-132 (carboxyethylgermanium sesquioxide)

added in the cultures of either
purified peripheral monocytes or U937 human
myelogenous leukemia cells did
not produce any significant effect on expression of
either HLA-DR antigens
or FcR1 on the cell. Incubation of peripheral blood
mononuclear cells

(PBMC) with Ge-132, however, produced a factor
inducing augmentation of
HLA-DR and IgG-Fc receptor (FcR1) expression on
the monocytes or U937.

Pretreatment of this PBMC culture fluid with pH 2.0
or specific antiserum
against human interferon .gamma.(IFN.gamma.)
resulted

in a marked redn. of both HLA-DR and FcR-inducing
activities, suggesting
that a major factor induced by Ge-132 in the PBMC
may be IFN.gamma..

Ge-132 may stimulate PBMC to produce a sol.
factor (IFN.gamma.),
which in turn augments the expression of HLA-DR
antigens and FcR1 on the cell of myelogenous or
macrophage series.

L4 ANSWER 76 OF 79 MEDLINE

DUPLICATE 47

ACCESSION NUMBER: 87035442 MEDLINE

DOCUMENT NUMBER: 87035442 PubMed ID:
2430045

TITLE: Production of a cytokine with interleukin 3-like properties and cytokine-dependent proliferation in human autologous mixed lymphocyte reaction.

AUTHOR: Suzuki R; Suzuki S; Takahashi T; Kumagai K

SOURCE: JOURNAL OF EXPERIMENTAL MEDICINE, (1986 Nov 1) 164 (5) 1682-99.

Journal code: 2985109R. ISSN: 0022-1007.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 198612

ENTRY DATE: Entered STN: 19900302

Last Updated on STN: 19900302

Entered Medline: 19861203

AB The autologous mixed lymphocyte reaction (AMLR) was assayed in a medium containing fresh autologous serum, by using nylon-adherent stimulator cells and nonadherent responder T cells, which were prepared from human peripheral blood mononuclear cells in the absence of fetal calf serum (FCS) to avoid any sensitization to xenogeneic protein antigens. DNA replication without a background proliferative response was induced by stimulator cells in the responder cells. The addition of monoclonal anti-HLA-DR antibody to the culture or treatment of the responder cells with complement plus anti-T4 but not anti-T8 monoclonal antibody suppressed the AMLR, suggesting that this specific AMLR involves an interaction between HLA-DR antigens and helper/inducer T cells. Regardless of this specific DNA replication, the AMLR generated no production of interleukin 2 (IL-2) and interferon gamma (IFN-gamma), both of which could be found in the allogeneic (allo) MLR. In addition, DNA replication in the AMLR was not inhibited by the addition of specific antisera for IL-2 and IFN-gamma, both of which significantly inhibited the DNA replication in allo-MLR. The AMLR was accompanied by production of a soluble factor, which could stimulate the proliferation of murine interleukin 3 (IL-3)-dependent cell line 32Dcl but not the proliferation of IL-2-dependent cell lines. This factor was also found to be responsible for proliferation of responder nonadherent cells in the AMLR. It strongly stimulated bone marrow cells, as did the murine IL-3. The factor had an Mr range, as determined by gel filtration, of 15,000-28,000, but it did not bind to fast protein liquid chromatography (FPLC)-MonoQ column. Thus, the

factor is distinguishable from IL-2 in physicochemical or biological properties, but similar to murine IL-3. These results suggest that the human AMLR may be primarily a phenomenon in which non-T cells mediated by the HLA-DR antigens on the cell stimulate helper/inducer T cells to produce a lymphokine with IL-3-like properties, but no IL-2, which in turn stimulates the factor-dependent cells to proliferate.

L4 ANSWER 77 OF 79 MEDLINE

DUPLICATE 48

ACCESSION NUMBER: 86087152 MEDLINE

DOCUMENT NUMBER: 86087152 PubMed ID: 3484491

TITLE: Antigen presentation by human dermal fibroblasts:

activation of resting T lymphocytes.

AUTHOR: Umetsu D T; Katzen D; Jabara H H; Geha R S

CONTRACT NUMBER: AI20373 (NIAID)

AI21163 (NIAID)

AM31925 (NIADDK)

+

SOURCE: JOURNAL OF IMMUNOLOGY, (1986 Jan) 136 (2) 440-5.

Journal code: 2985117R. ISSN: 0022-

1767.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals

ENTRY MONTH: 198602

ENTRY DATE: Entered STN: 19900321

Last Updated on STN: 19970203

Entered Medline: 19860205

AB We have shown that human dermal fibroblasts, exposed to interferon -gamma (IFN-gamma) to induce surface class II major histocompatibility complex (MHC) antigens, were capable of presenting tetanus toxoid (TT) antigen to human TT-specific T cell clones. Antigen presentation by fibroblasts was antigen dependent, required HLA-DR expression by fibroblasts, and was MHC restricted. In contrast, we now report that IFN-gamma-treated fibroblasts are unable to present TT antigen to purified resting T cells obtained from the peripheral blood of TT-immune donors. In addition, although IFN-gamma-treated fibroblasts were able to stimulate alloreactive T cell clones, they were unable by themselves to stimulate primary allogeneic responses in resting T cells. The failure of fibroblasts to stimulate resting T cells was not due to suppressor effects by fibroblasts, because induction of TT and alloantigen responses in resting T cells by monocytes

was not inhibited by the presence of fibroblasts. On the contrary, IFN-treated fibroblasts were synergistic with small numbers of monocytes in activating resting T cells. In addition, the failure of antigen presentation by fibroblasts to resting T cells was reversed by the addition of recombinant human interleukin 2 (rIL 2) to cultures, but not of purified human interleukin 1 (IL 1). These results emphasize that the requirements for activation of resting T cells differ from those of T cell clones. Although fibroblasts can efficiently present antigen to T cell clones, antigen presentation by fibroblasts to resting T cells requires the addition of exogenous IL 2. It is postulated that fibroblasts differ from classical antigen-presenting cells in that fibroblasts are incapable of stimulating the production of IL 2 in resting T cells.

L4 ANSWER 78 OF 79 MEDLINE
DUPLICATE 49

ACCESSION NUMBER: 86060842 MEDLINE
DOCUMENT NUMBER: 86060842 PubMed ID:
3934267

TITLE: Antigen presentation by interferon-gamma
-treated endothelial cells and fibroblasts:
differential ability to function as antigen-presenting
cells despite comparable Ia expression.

AUTHOR: Geppert T D; Lipsky P E
CONTRACT NUMBER: AM09989 (NIADDK)
SOURCE: JOURNAL OF IMMUNOLOGY,
(1985 Dec) 135 (6) 3750-62.
Journal code: 2985117R. ISSN: 0022-
1767.

PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL
ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals;
Priority Journals
ENTRY MONTH: 198512
ENTRY DATE: Entered STN: 19900321
Last Updated on STN: 19970203
Entered Medline: 19851223

AB The effect of interferon-gamma (IFN-gamma) on endothelial cell (EC) and fibroblast (FB) class II major histocompatibility complex (MHC) gene product expression and antigen presenting ability was examined. Control FB did not express class II MHC gene products, whereas a small (less than 1%) population of passaged EC expressed class II gene products. IFN-gamma induced a comparable density of HLA-DR expression on nearly all EC and FB. IFN-gamma-treated EC and FB also expressed HLA-DP but at a lower density, whereas HLA-DQ expression was barely detectable on either cell type. Control FB were not able to stimulate allogeneic T4 cell DNA

synthesis or function as antigen-presenting cells (APC). Control EC were also unable to stimulate allogeneic T4 cell DNA synthesis unless large numbers of stimulator cells were used. Small numbers of IFN-gamma-treated EC were able to stimulate allogeneic T4 cell DNA synthesis, whereas larger numbers were markedly more effective than control EC. In contrast, IFN-gamma-treated FB were ineffective stimulators of allogeneic T4 cell DNA synthesis. IFN-gamma-treated FB were able to present the exogenous antigen SKSD to autologous but not allogeneic T4 cells, but they were extremely inefficient APC. The inability of IFN-gamma-treated FB to function as APC could not be explained by FB-mediated immunosuppression, Ia density, or HLA-DQ expression. This limited capacity of IFN-gamma-treated FB to participate in Ia-restricted functional interactions with T4 cells correlated with a similar diminished capacity to support nonspecific mitogen-induced proliferation of T4 cells before IFN-gamma-induced Ia expression. This accessory cell function was not enhanced by IFN-gamma treatment. Monocytes synergistic to the responding T4 cells but not interleukin 1 (IL 1) permitted IFN-gamma-treated FB but not control FB to stimulate allogeneic T4 cell DNA synthesis, but they remained markedly less effective stimulators than monocytes. Moreover, IFN-gamma-treated FB were effective stimulators of alloprimed T4 cells, in contrast to their inability to stimulate fresh T4 cells. Furthermore, monocytes and IFN-gamma-treated FB were comparably effective stimulators of alloreactive T cell lines. These data suggest that accessory cells perform functions unrelated to Ia and IL 1 that are necessary for mitogen-, alloantigen-, and antigen-induced proliferation of freshly isolated T cells. Monocytes and EC effectively perform this function, but FB do not. This accessory cell function does not seem to be as important for the activation of primed T cells.

L4 ANSWER 79 OF 79 MEDLINE

DUPLICATE 50

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AUTHOR: Becker S
CONTRACT NUMBER: CA29589 (NCI)
CA33003 (NCI)

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AB The development of HLA-DR (Ia) expression in the presence and absence of interferon-gamma was monitored in monocyte-macrophage cultures. Overnight incubation with doses as low as 5 U/ml gave elevated values for Ia expression and the maximum increase was obtained with 200 U/ml. In contrast interferon-alpha had only a slight effect on the expression of Ia at doses as high as 2000 U/ml. The increase seen at 24 hr was maintained during the first 2 days of culture. The interferon-gamma-treated cells expressed four to five times more Ia than fresh monocytes. During the same time, monocytes cultured in the absence of interferon expressed approximately two times the amount of fresh monocytes. When the surface density of Ia was calculated, the interferon-gamma-treated monocytes expressed twice that of the untreated cells. Major changes in morphology and size occurred between days 3 and 4 of monocyte to macrophage development. Consequently a rapid increase in Ia expression took place; however, when the surface density was calculated this value increased only slightly when the monocytes matured to macrophages. The interferon-gamma-treated cells continued to express more total Ia as well as having increased surface density of this antigen. Interferon-gamma was also added to monocyte-macrophages several days after culture initiation (days 3, 4, and 5). Despite being in different stages of maturation, the cells responded to the interferon with increased Ia expression and surface density. The phagocytic activity of opsonized zymosans was also monitored. In contrast to Ia expression, this activity was downregulated by interferon-gamma, and the lower levels of phagocytosis were maintained through the 7 days of observation. Thus, interferon-gamma appears to change the differentiation pathway of the monocyte. The signal stimulates an increased level of Ia that may assist in the initiation of immune

responses, and at the same time downregulates the scavenger role of removing opsonized particles. Once the monocyte has received this specific signal it continues to develop in a pathway different from that of the nontreated monocytes.

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